

# HUMAN PHYSIOLOGY

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E.B. Babsky, B.I. Khodorov,  
G.I. Kositsky, A.A. Zubkov

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## About the Book

HUMAN PHYSIOLOGY is a textbook in two volumes for medical students which gives a concise and comprehensive account of physiology in its contemporary state. The most important theoretical conceptions of the nature of the main physiological processes are discussed, and the facts underlying these conceptions presented. Bearing in mind that the book is intended for medical undergraduates, the authors considered it possible to dwell upon certain pathological data that would assist understanding of the importance of the various physiological processes occurring in the body. The first volume contains the following sections: General Principles and Basic Conceptions of Physiology; Blood; Circulation; Respiration; Digestion; Nutrition. Metabolism and Energy Exchange; Excretory Processes; Internal Secretion.

The textbook was written by a group of eminent specialists with a vast experience in research and as teachers, under the editorship of Evgeni Babsky, Member of the Ukrainian Academy of Sciences.



BABSKY  
KHODOROV  
KOSTESKY  
ZUBKOV

HUMAN PHYSIOLOGY

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Е. Б. Бабский,  
А. А. Зубков, Г. И. Косицкий,  
Б. И. Ходоров

**ФИЗИОЛОГИЯ  
ЧЕЛОВЕКА**

под редакцией  
академика АН УССР

Е. Б. БАБСКОГО

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# **HUMAN PHYSIOLOGY**

**by**

**E. Babsky, B. Khodorov, G. Kositsky,  
A. Zubkov**

**Edited**

**by**

**E. B. BABSKY,**

**Member of the Ukrainian Academy  
of Sciences**

**Translated from the Russian**

**by**

**LUDMILA AKSENOVA**

**Translation Edited**

**by**

**H. C. CREIGHTON**

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# Chapter 1

## INTRODUCTION

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### THE SUBJECT MATTER AND METHOD OF PHYSIOLOGY

**The subject matter of physiology.** Physiology is one of the most important branches of *biology* and is concerned with study of the functions, i. e. the living processes of organisms, and of their organs, tissues, and cells, and of the structural elements of cells. For a comprehensive and deep understanding of functions physiology strives to reveal all their properties and phenomena, their interrelations and the changes occurring in different environments and with various conditions of the organism itself. Physiology studies both the species and individual development of functions and their alteration and adaptation to the continuously changing conditions of their environment.

The final aim of physiology is to acquire the deep understanding of functions that ensures the possibility of actively influencing them in any desired direction.

**Classification of the physiological disciplines.** Animal physiology is divided into several separate disciplines which, though quite independent, are closely interconnected. General, comparative, and special physiology are primarily distinguished.

*General physiology* studies the laws governing the response of living matter to the effect of its environment, the principal vital processes inherent to any organism, and the qualitatively peculiar phenomena that are responsible for the difference between living

and non-living matter. One of the branches of general physiology is *cell physiology*.

Comparative physiology investigates the specific peculiarities of the functions of organisms of different species, and of organisms of the same species at different stages of individual development. The final purpose of comparative physiology, which in our time is becoming transformed into *evolutionary physiology*, is study of the laws of the species and individual development of functions.

Along with general physiology and evolutionary physiology, which generalize the entire range of physiological data, there are special or particular branches, such as the physiology of separate animal classes and animal groups (for example, farm animals, birds, insects), or the physiology of individual species (for example, sheep, cows, etc.), the physiology of individual organs (for example, the liver, kidneys, and heart) and tissues (for example, nerves or muscular tissue). Branches of physiology concerned with the study of individual functions are often distinguished so that we speak of the physiology of circulation, digestion, etc., as particular fields of science. There are as many branches of special physiology in fact as there are different groups of living organisms, different organs and tissues, and, finally, different types of activity of living organisms. The difference in the processes studied is due to the morphological features of the objects examined, to the variety of their conditions of existence, and to many other factors.

The physiology of man and the higher animals is the most studied branch of special physiology.

*Human physiology* has its own branches, which are of great practical importance: e. g. the physiology of work, physiology of physical exercise and sport, physiology of nutrition, and physiology of old age.

*Pathological physiology* is a particular, special branch of physiology with its own specific problems. As distinct from *normal physiology*, which is concerned with the vital processes occurring in a healthy body, it studies the general laws governing the causation, development, and course of pathological processes in the organism, i. e. the peculiar phenomena of the vital activity of a sick organism that distinguish it from a healthy one.

**Physiology and the other sciences.** Physiology is closely linked with a number of other fields of knowledge, basing its investigations on the data of some of them, and providing, in turn, the ground for the development of others.

Physiology constantly draws on the laws of physics and chemistry and widely employs their methods of research since every vital process involves conversion of matter and energy, i. e. physical and chemical processes. Thus, two trends of research in physiology, physical and chemical, have become extremely important; they have yielded much factual material, revealed the peculiar features

governing the physical and chemical processes in organisms, and elaborated special methods and techniques for their examination. Therefore the physical and chemical trends in the study of vital phenomena have become independent scientific disciplines, *biological physics* and *biological chemistry*.

An important division of the biophysical trend is *electrophysiology* which studies the electrical phenomena encountered in the animal organism with excitation of the nerve, muscle, and gland tissue.

Biophysics and biochemistry study specific physical and chemical phenomena of the vital activity of an organism and of its parts, i. e. the elements of a single common whole, the physiological function. They offer great possibilities for analysing vital phenomena, but neither of them alone can provide full knowledge of functions, which can be gained only by physiological studies based on a synthesis of physical, chemical, and biological data.

Physiology is closely linked with the morphological sciences — anatomy, histology, and cytology — since morphological and physiological phenomena are inseparable. The shape and structure of an organism, and of its parts, and their functions are mutually conditioned; the functions of an organism, or of its organs, tissues, or cells, cannot be studied deeply without knowing their macroscopic, microscopic, and submicroscopic structure and the changes that occur in that structure during performance of the function being investigated.

Physiology also rests upon general biology, the theory of evolution and embryology, since study of the vital activity of any organism requires knowledge of the history of its development, both phylogenetic and ontogenetic. At the same time, study of the evolution of functions helps to solve certain problems of evolution itself.

*Cybernetics*, the science dealing with the general principles of control and communication in machines, mechanisms, and living organisms, has acquired great importance in physiology in recent years. It employs mathematical methods and simulation (i. e. simplified theoretically constructed schemes of physiological processes), and artificial mechanisms that reproduce phenomena identical in certain properties with those occurring in the body. Artificial models always simplify and intentionally schematize the biological phenomena they represent, but they do aid in understanding of some internal links existing between various processes, allow us to check the soundness of certain theories, show the way in which that may be done, and in many cases suggest what new experiments are required. The cybernetic approach to the investigation of physiological problems gives wide synthetic coverage of the phenomena encountered in complex systems (living organisms are just such systems) and helps to reveal the general principles underlying the control of various functions, as well as the interactions existing between them.

Physiology is closely linked with all the branches of medicine, and, as Pavlov put it, "fundamentally understood physiology and medicine are inseparable". The advances made in physiology are constantly used by medicine where physiology always finds the widest field of application. Only through knowledge of the physiological processes taking place in the normal healthy organism can we understand the functional disturbances encountered in the body with various diseases and plan correct measures for treatment and prevention. Many examples could be given to illustrate the use of the advances of physiology in medical practice. Thus, the elaboration of physiology of digestion by Pavlov enhanced understanding of the diseases of the gastrointestinal tract, and served as the basis for a powerful therapeutic measure — dietetics, the study of vitamins provided means for the successful control of such diseases as scurvy and rickets; the discovery of the pancreatic hormone insulin, and the elaboration of methods to produce it, has saved the lives of thousands of diabetic patients; research into blood groups provided the basis for such a valuable procedure for medical practice, as blood transfusion.

In turn, medicine has supplied physiology with extremely valuable material. The study of various human diseases has contributed to an understanding of the mechanisms of many normal physiological processes, and helped to ascertain the functions of certain organs. Pavlov wrote in this regard: "The world of pathological phenomena is an infinite series of various peculiar (i. e. not encountered under normal circumstances) combinations of physiological phenomena, or, as it were, a series of physiological experiments conducted by nature and life. The combinations are often such as could not enter the head of the contemporary physiologist for a long time, and in some cases could not even be deliberately reproduced by the techniques available to him." The clinic poses new problems for physiological experiment, but at the same time is itself a rich source of new physiological facts. Therefore a new particular branch of physiology (clinical physiology) is in process of formation, which strives to apply the theoretical, experimental, and methodological advances of physiology to the clinic, and to explain and analyse, with the help of clinical observations, the physiological processes occurring in the human organism.

The importance of physiology in medicine, and of medicine in physiology, is so great that Pavlov was absolutely justified in seeing the need for "a valid and fruitful union of medicine and physiology, those two forms of human activity that are building the science of the human body and that promise to ensure man in the future his true happiness, health and life".

Physiology is also linked with modern psychology and pedagogy, particularly Pavlov's work on higher nervous activity, and is the scientific basis of these two subjects. The concrete practical impor-

tance of physiology in pedagogy is that the pedagogue must understand the age peculiarities of the physiological process taking place in the organisms of children in order to organize their activities and living correctly, and to adopt rational educational measures.

**Methods of physiological research.** Physiology is an *experimental science*. Observing and studying living phenomena, the physiologist attempts first to characterize them qualitatively and quantitatively, i. e. to describe and measure them accurately or, in other words, to express them in number and volume, and second, to document the results of his observations. Documentation usually consists in registering the results obtained in the form either of written records, films, or photographs, or of automatic recordings of the changes occurring in time in the process being studied (on film, moving paper, magnetic tape, etc.).

Both the measurement and the documentation require special instruments, devices, and apparatus corresponding to the problem studied. At times they are extremely complicated. Many devices for recording and measuring were already in use in physiological laboratories in the last century, but particular progress has been made in experimental techniques employed in physiological research today through wide use of devices embodying the advances of physics, chemistry, electronics, and cybernetics.

Physical, chemical, and technical methods and instruments provide physiological laboratories with research equipment that enables information on functions and processes occurring in the organism and in its organs, tissues, and cells, to be obtained. The precise and highly-sensitive apparatus used by the modern physiologist greatly extend the perceptive faculties of man, increase the resolving power of his sense organs, and make observation of numerous physiological processes possible. But even the most refined and precise methods of observation are not sufficient to understand the nature of vital phenomena.

The physiologist cannot be satisfied with observations alone, since they only supply the answer to the question *what is occurring* in the body, while he is also trying to find out *how and why physiological processes occur*. That requires *experiments* providing observations under altered conditions produced and changed by the experimenter himself.

In experimental study of any process in the organism the physiologist is trying to establish the conditions, which, when reproduced, will give rise to the given process, or will intensify or weaken it. In that way, he acquires knowledge of the causes of one process or another, of its nature, and of the way to control it.

The forms of physiological experiments are very diverse and are determined by the aims of the research. Thus, the influence of the external environment on an organism is studied by placing it in surroundings in which the gas composition, temperature, or

humidity of the air are changed or the conditions of illumination altered, or by changing the nutrition of the organism, by exposing it to ionizing radiation, ultra-violet rays, ultra-sonic vibrations, and to other factors. For precision of analysis, only the factor studied is changed during the experiment, only one effect is applied, and the experiment is conducted "with all other conditions identical", i. e. with all the other conditions of the experiment, except that studied, unaltered.

To ascertain the function of a particular organ and its importance to the organism, physiologists either remove it completely or in part (*extirpation*) or transplant it to a new site (*transplantation*), and then observe what consequence that has for the organism. These methods have proved particularly valuable in studies of the endocrine glands. To study the influence of the nervous system on an organ, the nerve fibres supplying it are cut or blocked (*denervation*). To sever the connection of an organ with the vascular system its various blood vessels are either cut off by being tied (*ligation*) or are anastomosed by suturing the central end of one to the peripheral end of the other (*vascular anastomosis*). The activity of organs that lie deep in the body and are therefore not observed directly is studied by means of fistulas. One variant of the method involves the introduction of a plastic or metal tube into the cavity of the organ, for example into the stomach, intestine, or urinary bladder, with its other end fixed to the skin; with the other variant gland ducts are brought out to the surface of the body. For research a thin tube, or catheter, is introduced into the heart, blood vessels, or gland ducts, with its other end connected to various instruments either to record the organ's activity or to infuse various substances (*catheterization*). To artificially excite an organ's activity, physiologists use stimulation by means of electrical, mechanical, chemical, or other factors.

Most of the research methods mentioned require an incision or a surgical operation on a living subject, and are employed in both acute and chronic experiments. In *acute experiments*, or *vivisections*, which usually are of short duration, the animal is either anaesthetized or immobilized by some other method, and then opened by an incision so as to study the activity of organs or to observe the effect on them of stimulation of a nerve or the introduction of drugs, etc. In *chronic experiments* physiologists subject an animal to various surgical operations and begin their studies only after it recovers from the procedure. Not infrequently, it is possible to observe the animal so operated on for many weeks, months, or years.

The function of organs is studied not only in the intact organism, but also *isolated* from it. Solutions, the composition of which is controlled by the experimenter, are passed through the vessels of a resected, or isolated, organ (*perfusion*) and the environmental

conditions required by living tissue are provided (definite temperature, humidity, etc.).

All these methods help to fathom the nature of the processes taking place within an organism. At the level of the cell and even of its parts they are analysed in microphysiological experiments, when the object of research is, for example, a single cell, muscle, nerve, etc.

Analytical research is aimed at studying every physiological process that occurs in an organ, tissue, or cell in isolation from all the other processes taking place in the organism. Then a comprehensive idea of the given process alone, of the function of one individual organ, tissue, or cell can be obtained, but that does not give a correct and complete understanding of the vital activity of the organism. Research has to be conducted in the direction of what Pavlov called "synthetic physiology" as opposed to "analytic physiology" which studies separate organs, tissues, and cells. In his view, the aim of synthetic physiology was to study the organism in all its links and interrelations with its external environment. In that type of research the physiologist seeks to approximate the conditions of the organism studied as closely as possible to its natural ones.

An important aspect of synthetic research is that all activities of the animal or human organism are studied from the point of view of their subordination to the nervous system, a trend in research known as the *principle of nervism*. It is an integral part of synthetic studies because the nervous system and its higher part, the cerebral cortex, is the system of the organism that unites all its parts and governs its relations with its environment. It follows from that that synthetic study of an organism with a nervous system is only possible if the role of nervous control is taken into account.

The main objects of physiological experiments are animals of various kinds. Opportunities to experiment on human beings are extremely limited as they cannot be exposed to effects that may prove harmful. Moreover, the possibilities afforded for observing and recording many of the processes of the human organism were comparatively few until recently; the arsenal of research methods used in the past in experiments on animals could not be employed by the physiologist and for that reason the information on the function of many organs was limited to data provided by experiments on animals. That situation, however, has now changed.

The current advances of physics, radio engineering, electronics, and cybernetics, have been of great help to physiologists and doctors in the study of the functions of both the healthy and the sick human organism. New methods of functional study have been elaborated, and old ones modified, and it has become possible to study many

phenomena without inflicting any harm to the subject. Thus, electrical processes occurring in the body are studied by applying electrodes to its surface and employing electrical recording instruments; the records obtained provide evidence of the condition and activity of the nervous system, the skeletal muscles, heart, and other organs. Electrical methods also make it possible to study mechanical, sound, temperature, and other processes in the organism.

The use of *radiotelemetry*, i. e. the transmission of physiological information from the subject of investigation by means of radio waves from a distance, has been a great methodological advance in physiological research. The device that records the phenomenon examined, the *pick-up*, is applied to the human subject or animal and connected to a special transmitter placed directly on or close to the subject. The action of a definite physiological process changes the electrical parameters of the pick-up, which causes changes in the rate or amplitude of the high-frequency electromagnetic oscillations produced by the transmitter. Its signals are picked up by a radio receiver located at a distance from the subject. The physiological processes occurring during muscular activity or physical exercise and sport are studied in that way, for example, it is also employed to keep a check on astronauts during space flights.

Simultaneous recording of the many and various physiological, physical, and chemical processes occurring in the different cells, organs, and systems is exceptionally important for investigating the activity of an intact human or animal organism. Modern techniques have made that possible, which has given rise to the complex problem of rapid processing of all the data obtained, and of revealing the pattern of their relationships. Physiologists have therefore now began to use electronic computers to analyse and process physiological data, which has already yielded important new results.

#### HISTORICAL OUTLINE OF THE DEVELOPMENT OF PHYSIOLOGY

Attempts to understand the vital activity of the human and animal organism have been made since the dawn of civilization. Ideas on anatomy and physiology are to be found in the works of the philosophers and physicians of ancient China, India, Greece, and Rome that have come down to us. Together with separate correct observations they also expressed many fantastic assumptions and delusions. No scientific study of the body existed either in antiquity (although experiments on animals were attempted) or in the Middle Ages when attempts to understand nature, and study the structure and functions of the human body were cruelly persecuted by the Church.

## THE ORIGIN AND DEVELOPMENT OF EXPERIMENTAL PHYSIOLOGY IN THE SEVENTEENTH AND EIGHTEENTH CENTURIES

As a science employing the experimental method of research physiology stems from the works of *William Harvey*, the English physician, anatomist, and physiologist whose *discovery of the circulation of the blood* "made physiology (both human and animal) a science," as Engels put it. Harvey's famous work *Exercitatio Anatomica de motu cordis et sanguinis in animalibus* published in 1628 gave a correct conception based on numerous observations and experiments of the greater and lesser circulation, and of the heart as the organ that forces the blood around the body. The discovery of circulation was a powerful stimulus for the development of physiology; it arose from the revolution in ideology occurring at that time and the whole complex of social phenomena of the time.

The sixteenth and seventeenth centuries were a period of social-economical change in Europe in which feudalism was being replaced by capitalism. The rise of capitalism was associated with the extension of trade, the discovery of new markets for buying raw materials and selling goods, and with the development of navigation and means of communication. That encouraged the development of such sciences as astronomy, mathematics, and mechanics, without which accurate orientation in time and space was impossible. Their rapid progress led to an upheaval in ideology, which affected the development of all sciences, including physiology. The upheaval reflected the revolutionary spirit of the age and gave rise to a new attitude with regard to scientific research. The cause and simultaneously the result of this new attitude were a) weakening of the faith in the Church and in the works of classical authors whose authority paralysed minds and made them see non-existent phenomena, and b) the introduction into science of the inductive method of investigation, based on accurate observation and experiment.

This new trend was proclaimed by Francis Bacon, a materialist philosopher, whose ideas greatly influenced the development of natural science. Following Bacon's views, Harvey declared that any learning required diligent observation and frequent counsel with the senses and that one should not rely on the experiments of others but should conduct one's own; otherwise one would never become a researcher in any branch of natural science. On these views experimental methods for investigating physiological processes were evolved and yielded new scientific discoveries.

In that period, and later, examination of the structure and functions of the human body, and the study of anatomy and physiology, were greatly stimulated by the needs of practical medicine. Infectious diseases were widespread in Europe not unassociated with the development of means of communication, distant voyages in search of new markets, the migration of populations over great

distances, and the growth of towns. Medicine was faced with the problem of evolving measures to prevent epidemics and to discover methods of treating diseases, which required knowledge of both the structure and the functions of the human body.

Progress in anatomy preceded advances in physiology because an understanding of the structure of the body and its organs was necessarily a prerequisite for functional studies. Investigations conducted in the sixteenth century by the founder of anatomy, Vesalius, and by Servetus, Colombo, Falloppio, and other anatomists, laid the foundation for physiological discoveries, in particular the circulation of the blood. All further advances in physiology, especially in its first period of development (between the seventeenth and eighteenth centuries) were inseparable from anatomical advances. Thus for example, the discovery of the lymphatic vessels led to an understanding of lymph flow; the discovery of capillaries by Leeuwenhoek and Malpighi proved that the conception of the circulation of the blood was correct, and provided the basis for comprehension of the role of blood in metabolism; study of gland structure provided the possibilities for investigating their function, etc.

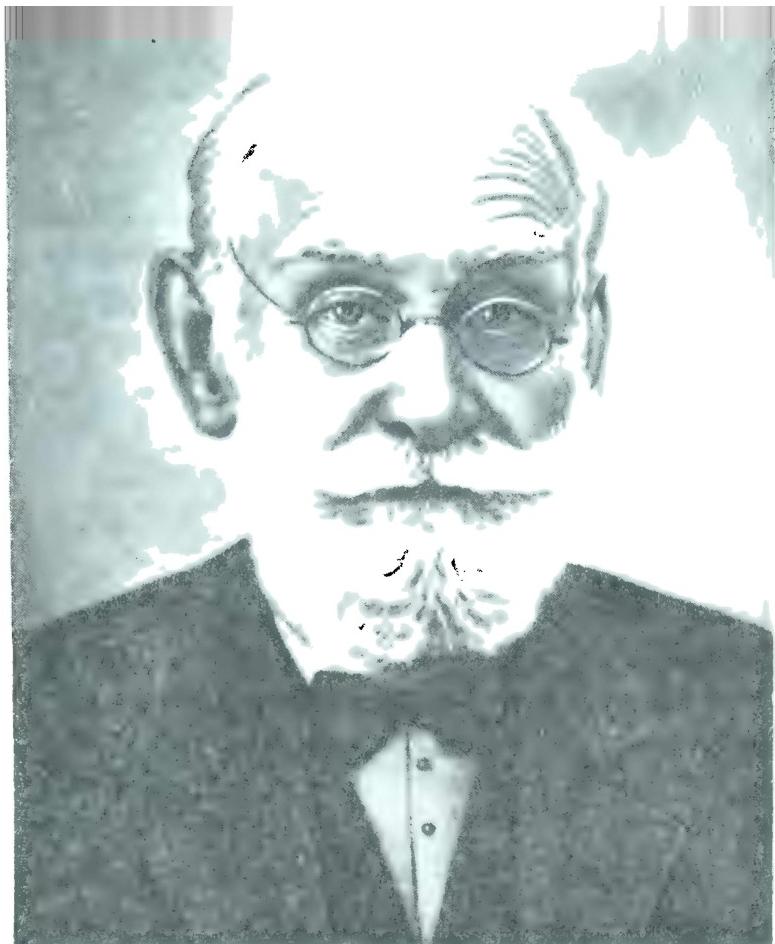
The discovery of the reflex by Descartes in the first half of the seventeenth century was of greatest importance.

Descartes supposed that the effect of a stimulus on a sense organ was to stretch the nerve threads that ran to the brain and caused the opening of orifices on the internal surface of the brain through which "animal spirits" harboured in the cerebral ventricles escaped and passed along the nerves like flames, and flowed into the muscles, causing them to contract. In his opinion, some human reactions, like jerking a leg away from a flame, occurred through that mechanism, while voluntary movements were governed by the soul, lying in the pineal body of the human brain. Although Descartes' idea of the nature of body reactions to stimulation now seems naive, it must be admitted that he did describe the reflex act and the pathway along which the nerve impulse passed during a reflex. As for the term "reflex", it was introduced at the end of the eighteenth century by the Czech scholar G. Prochaska.

The anatomical trend prevailed at that period in physiology, but investigations associated with physics and chemistry, which had then begun to develop, were already of some importance to it; attempts were made to introduce physical methods of investigation and to adopt the laws of mechanics, physics, and chemistry to explain bodily phenomena.

Two trends arose in science in the seventeenth century and became known as the iatrophysical and iatrocchemical schools. The adherents of the former believed that the laws of mechanics and physics gave an exhaustive explanation of all vital phenomena. Thus, Borelli the author of the work *On the Motion of Animals* claimed that the actions of animals occurred as the consequence of, by means of,

**Ivan Pavlov**  
**(1849-1936)**



**Ivan Sechenov**  
**(1829-1905)**





and on the basis of mechanical phenomena and that anatomy, physics, and mathematics underlay all vital processes.

Of all the studies conducted in the seventeenth and eighteenth centuries and associated with mechanics, physics, and chemistry, most important for physiology were Borelli's work on the mechanism of respiratory movements and the role of the diaphragm, and his application of the laws of hydraulics to study of blood flow in the vessels; the work of Hales, who detected the existence of the blood pressure; Scheiner's study of the eye from the point of view of optics, his investigation of the refractive media of the eye, and his demonstration of the role of the retina in the origination of the visual sense; the works of Réaumur and Spallanzani on the chemical mechanism of digestion; the studies of Lavoisier, who put ideas about the respiratory processes on a scientific basis, and who jointly with Laplace was the first to measure the energy expenditure of the body; and the first detailed investigation of the phenomena of excitability and sensitivity made by Haller, and the discovery of bioelectrical phenomena by Galvani, who founded electrophysiology, were also among the most important contributions. Of great significance also were the discoveries and ideas of the eminent Russian naturalist Lomonosov, the value of which was only realized later. Lomonosov was considerably in advance of the ideas of his age, and in 1748 formulated the general law of nature, the law of the conservation of matter and motion, which in the nineteenth century became the basis for the most essential physiological studies of metabolism and of the conversion of energy in the body. Lomonosov affirmed convincingly and persuasively that physics and chemistry in particular were very important for physiology and insisted that the physiologist "must supply from physics the factors responsible for the motion of an animal body" and that "a doctor without adequate knowledge of chemistry could not be perfect."

Metaphysical ideas prevailed in the seventeenth and eighteenth centuries. The idea of development was alien to science; all natural phenomena were regarded as constant and invariable. The metaphysical character of science was reflected by the mechanistic concepts that dominated at that time, and by the idealist, vitalist conceptions that flourished at the end of the eighteenth century, ideas that deeply influenced the study of physiological problems. Thus, mechanism was vividly displayed in the works of certain philosophers and physiologists, like Lamettrie, who proclaimed that the organism was a machine.

#### THE DEVELOPMENT OF PHYSIOLOGY IN THE NINETEENTH CENTURY

Great changes occurred in the natural sciences in the nineteenth century, when physiology, separated off from anatomy and histology, became a completely independent science, and made immense

progress. A number of remarkable achievements and discoveries made in contiguous branches of knowledge were of essential importance, such as the *advances in organic chemistry, the substantiation of the law of the conservation and conversion of energy, the discovery of the cell, and the foundation of the theory of the development of the organic world.*

The discovery of the law of the conservation of energy in the 1840's by Mayer, Joule, and Helmholtz (which was a further elaboration of the law of the conservation of matter and motion formulated a hundred years previously by Lomonosov) provided a sound foundation for the study of the conversion of energy in a living body. The problem of the energy displayed in the activity of a human or animal body, long a mystery, was cleared up. The cycle of energy in nature was understood; Timiryazev showed that the free energy of the sun rays is converted into the chemical energy of complex organic compounds formed in green plants in the process of photosynthesis. Those organic compounds are taken into the animal organism as food, and chemical energy is liberated through their breakdown and converted into kinetic forms of energy, thermal, mechanical, and electrical. Thus, plants accumulate latent, potential energy, and animals expend it in utilizing the energy liberated in the course of chemical breakdown of substances in their organisms.

In the second half of the nineteenth century the works of chemists enabled the amount of heat liberated by combustion of the main foodstuffs outside of the body to be estimated, i. e. enabled their caloric value to be determined. At the same time, physiologists evolved methods for measuring the amount of energy liberated by the body at rest and when performing work of various intensity (the methods of direct and indirect calorimetry proposed by Rubner, Pashutin, Likhachev, Benedict, and Atwater).

Through complex experiments, it was found in complete agreement with the law of the conservation of energy, that the amount of heat produced by the digestion of definite foodstuffs in the organism was equal to that liberated on their combustion outside of the body.

Apart from these methods of studying thermodynamic and energy phenomena, other physical methods elaborated in the nineteenth century for investigating the functions of living organisms played an important role in physiology. Valuable results were obtained through the introduction of methods of electrical stimulation and graphical recording of the activity of organs by means of such special instruments as the kymograph, myograph, sphygmograph, etc. Great credit is due to Du Bois-Reymond for his detailed elaboration of the method of electrical stimulation of living tissues by means of the induction apparatus proposed by him; to Ludwig, inventor of the kymograph and of instruments for measuring blood

pressure (the float manometer) and the velocity of blood flow (Ludwig's *stromuhr*; G. "stream clock"); to Sechenov who elaborated the method for extracting gases from blood; to Marey whose methods for studying movements and device for pneumatic recordings (Marey's capsule) greatly enriched physiology; and to Mosso who proposed the instrument for studying the filling of organs with blood (the plethysmograph), the instrument for studying fatigue (the ergograph), and the balance table for investigating the redistribution of the blood in the body. Pflüger discovered the laws governing the effect of direct current on excitable tissue, which were later radically revised and developed by Werigo. New methodological procedures enabled the study of the functions of nerves and nerve centres, the activity of muscles and the nature of their contraction, and the mechanism and innervation of the organs of respiration, circulation, excretion, etc. Investigations of the electrical phenomena encountered in the body, which were started by Galvani and Volta and continued by Du Bois-Reymond, Herrmann, and Vvedensky, brought us nearer to an understanding of the physiological process of excitation. Sechenov and Danilevsky were the first to study the electrical phenomena in nerve centres, a problem of particular interest to physiologists of the nineteenth century. Their need to study electrical phenomena in the nerves, muscles, and central nervous system is explained by the fact that the process of excitation is always associated with changes in the electrical potential of the stimulated tissue.

Physical methods of examination proved to be extremely helpful in studying the sense organs and the conditions of perception of the external world. Many extremely important facts were discovered in this sphere in the nineteenth century by Helmholtz and others, particularly facts pertaining to the physiology of vision and hearing; many original instruments for examining the receptors in the eye and ear were devised, and theories explaining the activity of those organs advanced. Precise methods for recording reactions made it possible to measure the performance of various physiological processes accurately. Even such rapidly occurring phenomena as the conduction of excitation along a nerve were measured quantitatively in space and in time (Helmholtz).

Nineteenth century advances in organic chemistry were of great importance for the development of physiology. The idea that the chemical compounds found in living organisms differed essentially from inorganic bodies, and that they could never be reproduced by the chemist outside of the body, was widespread at the beginning of that century. It was advocated by supporters of vitalism, an idealist, anti-scientific trend in biology, which held that there was some sort of non-material factor (or vital force) in the organism, animating it, and directing and regulating all biological processes. Johannes Peter Müller, the German physiologist, tried to substan-

tiate his idealist views with physiological data; he wrote that organic matter could never originate from a mechanical combination of non-organic particles brought together by chance, and that the synthesis could be effected only by the force that animates organic matter. Vitalist conceptions suffered a crushing blow in 1828 when a young chemist Friedrich Wöhler synthesized the first organic compound, urea, *in vitro*. Soon after, Liebig, one of the founders of organic chemistry, and then many other scientists synthesized numerous organic compounds, and studied the structure of a great number of those encountered in the body. A sound basis was thus provided for the chemical analysis of the metabolic processes occurring in living organisms.

The chemical composition of the body, the chemistry of digestion and respiration, and the composition and properties of the foods taken into the organism and of the breakdown products discharged from it, were studied in the nineteenth century.

Compared with the seventeenth and eighteenth centuries when the anatomical trend dominated, nineteenth century physiology was characterized by the prevalence of physico-chemical studies.

The most important feature of the nineteenth century science was the broad introduction of the theory of evolution, which had hitherto not had wide application or recognition in the biological disciplines. The theory of the evolution of the organic world was enriched by two works that marked a new epoch in biology, viz. Lamarck's *Philosophy of Zoology* and Darwin's *Origin of Species*. The discovery of the cell structure of organisms by the botanist Schleiden and the physiologist Schwann did much to introduce the theory of evolution into biology.

The recognition of the cell structure of plants and animals and of the fact that multicellular living organisms originate from an ovum opened the way for the formation and development of new branches of physiology. The study of cell structure helped to clear up many problems of the physiology of nerve, muscle, and gland tissues, and initiated cell physiology, the science of cell activity.

As Engels put it, the discovery of the cell proved to be "the fact that revolutionized all physiology and made possible comparative physiology". Darwin's theory was also a firm base for comparative physiology.

Studies concerned with the structure and functions of the cell and with the cellular structure of multicellular organisms posed an important and difficult problem before physiology: if a cell possesses its own metabolism, respiration, and excitability, and is capable of reproducing, how is the vital activity of an infinite number of cells united to form the activity of a multicellular organism; in other words, what is the relationship between the organism and the cells forming it? The problem became the arena of conflict between

several different trends. The supporters of the idealist trend in biology insisted that a non-material factor that supposedly governed the body united the activity of the separate cells, and was responsible for the unity and integrity of the body. That view was expressed extremely clearly in the middle of the century by the French anatomist and physiologist Henri Milne-Edwards who wrote that the harmony of all the parts of an organism depended not on the influence they exerted on one another, but upon their co-ordination by the will of a single principle, of an envisaged order, of a pre-existing idea. Similar ideas, that in essence are foreign to science, were propagated at the end of the century by the German biologist-vitalist Driesch.

A different point of view was defended by the supporters of the trend elaborated by R. Virchow, founder of pathological anatomy, who regarded the organism as a "sum of living units", i. e. cells, or as a "cell state". Virchow's followers considered each cell of a multicellular organism an "independent elementary organism", a conception that led Virchow and his disciples to believe that the function of the organism was the arithmetic sum of all its cell functions, and to belittle the idea of the integrity of the body.

In Virchow's opinion, the various pathological changes occurring in the body were manifestations of local diseases involving the cells of the given tissue; he overlooked the fact that purely local diseases that do not affect the entire organism, and that cause no pathological changes and reactions in it do not actually exist. The principal error of Virchow's theory of cellular pathology was his underestimation of the fact that the organism is a single whole whose functions cannot be regarded merely as the functions of the cells forming it, since their interaction and union give rise to qualitatively new phenomena.

The vitalist and idealist conceptions of the integrity of the organism, and Virchow's ideas, were opposed by nervism, a progressive, materialistic trend developed mainly by the Russian physiologists and clinicians Sechenov, Pavlov, Botkin, Ostromov, Bekhterev, and others. It was based on a conception of the integrity of the organism and of its parts being subordinate to the whole through the mediation of the nervous system. In human beings and animals, possessing nervous systems, that system controls and correlates all the functions of the organism, and adjusts the vital activity of the body as a whole to the environmental conditions. The fact that the cells of a multicellular organism possess the properties of metabolism, respiration, excitability, and reproduction peculiar to them, does not mean, from the stand-point of nervism, that they are independent organisms; their activity is subordinated to the organism as a whole.

The teaching of nervism was based on the vast number of facts collected over the entire nineteenth century. Research into nervous

control proved to be one of the most important achievements of that period. The nervous control mechanism of the functions of internal organs was demonstrated by many scientists (Magendie and Claude Bernard in France, Ludwig, Heidenhain and the Weber brothers in Germany, Walter, Cyon, Ovsyannikov, Mislavsky and Pavlov in Russia, Gaskell and Langley in England, and others) in experiments employing electrical and chemical stimulation, and dissection of various nerves. Those concerned with the innervation of the heart and blood vessels deserve special mention.

The Weber brothers discovered the inhibiting effect of the vagus nerve on the heart, Cyon the accelerative effect of the sympathetic nerve on cardiac contractions, and Pavlov the augmentative effect of this nerve on cardiac performance. Walter and then Bernard revealed the vasoconstrictive innervation, while some time later Bernard and a great many others discovered the vasodilatative innervation. Ludwig and Cyon discovered the afferent fibres that pass from the heart and aorta and cause reflex changes in cardiac activity and vascular tone. Ovsyannikov revealed the presence in the medulla oblongata of a centre that controls vascular tone, while Mislavsky studied in detail the respiratory centre also located there that had been earlier discovered by Legallois and Flourens.

Conceptions on the trophic function of the nervous system, on its influence on the processes of organ, tissue, and cell metabolism and nutrition, were suggested and demonstrated experimentally in the nineteenth century. These conceptions had been voiced by Magendie who described in 1824 the pathological changes encountered in the tissues after cutting of the nerves supplying them, by Bernard who observed the changes in carbohydrate metabolism following a puncture made in a definite area of the medulla oblongata (diabetic or Bernard's puncture), and by Heidenhain who showed the influence of the sympathetic nerve on the composition of the saliva. Pavlov determined the trophic effect of the nerves on the heart, and later generalized all the previously available facts into a teaching of the trophic function of the nervous system that was confirmed and developed in the present century.

The reflex theory of nervous activity was evolved in the nineteenth century. The spinal reflexes were studied at the beginning of the century and the reflex arc analysed, Magendie and Müller revealing the nature of the distribution of the efferent and afferent fibres in the spinal roots (Magendie's law). In the 1820's Flourens removed the cerebral hemispheres in experiments on birds and showed their role in the origination of sensations and voluntary movements.

The work of Sechenov who discovered the inhibition process in the central nervous system in 1862 and published his brilliant work *Reflexes of the Brain* in 1863 was of outstanding importance. In his book he developed the idea of the reflex nature of processes taking

place in the brain, including the most complex processes of human thinking, and thus laid the foundation for the physiology of higher nervous activity later elaborated by Pavlov.

Functional studies of various parts of the central nervous system were begun in the second half of the century, employing stimulation and removal of definite portions of the brain and spinal cord (experiments by Fritsch and Hitzig, Goltz, Munk, Bekhterev, Luciani).

The elaboration of surgical methods of physiological research was particularly important for the progress of physiology in the nineteenth century, i. e. the development of operative procedures that allowed chronic observation of the functions of various organs under relatively normal physiological circumstances. The method found particularly wide use with the introduction of anaesthesia, and the elaboration of rules of asepsis and antiseptics which protected the experimental animal from infection and provided for better healing of the wound and recovery from the operation. Dozens of different operations were devised during the century to study the functions of the various organs (Basov, Thiry, Vella, Heidenhain, Klemensiewicz, Pavlov). The modern physiology of digestion was developed by means of the surgical fistula technique, mainly by Pavlov and his pupils.

Physiological knowledge became essentially broader and deeper in the nineteenth century, particularly in the second half, and its progress contributed to the scientific foundation of the materialist philosophy with which natural science became greatly imbued at that time. Vitalism, the prevailing trend in biological sciences at the beginning of the century, had to surrender its position, though vitalist and other idealist conceptions will be found in the works of various authors published over the entire century. Thus, idealist doctrines were widely propagated among physiologists, particularly in Germany (physiological idealism, agnosticism, conditionalism, etc.).

Physiological idealism, founded by the famous German physiologist Johannes Müller, and so named by Ludwig Feuerbach, the philosopher-materialist, who criticized it, attempted to prove the anti-scientific conception that cognizance of the external world by means of the sense organs is not possible, alleging that they perceive only qualities inherent to them but not the actual reality that exists outside us. Agnosticism, advocated by Du Bois-Reymond, claimed that certain problems of natural science, including those of life and of human thinking would never be solved since they were incognizable. Conditionalism, represented in physiology by M. Verworn, denied that phenomena could be explained by their causes.

It was characteristic of the Russian physiologists of the second half of the century, it may be noted, that they were consistent up-

holders of materialistic views, owing to the powerful influence of the Russian materialist philosophers, Herzen, Belinsky, Pisarev, and Chernyshevsky.

#### PHYSIOLOGY IN THE TWENTIETH CENTURY

In the twentieth century physiology entered a new stage of development whose main feature was a change from a narrowly analytical approach to a broad synthetic understanding of vital processes. Pavlov's teaching on higher nervous activity was an essential advance which expanded the reflex theory, and on its basis revealed the nervous mechanism responsible for the most perfected and complex types of response of man and animal to the effects of their environment. The mechanism is the conditioned reflex, and the organ of higher nervous activity the cerebral cortex.

Jointly with his numerous pupils and collaborators, Pavlov studied the main processes occurring in the cerebral cortex and demonstrated experimentally that the cortex ensures both the most complex types of relationship of the body with its environment and the higher integration of the organism (i. e. of the functions of all its organs, tissues, and cells).

With the principles of the higher nervous activity of animals explained, investigation of the laws governing the cerebral activity of man became possible.

This gave rise to the theory of the two signal systems, the second of which is associated with speech and abstract thinking and is distinctive to man.

Pavlov, who founded a new trend in world physiology, was a staunch and consistent materialist, and affirmed that matter is primary and consciousness secondary. He maintained that "psychic activity is the result of the physiological activity of a definite mass of brain". His teaching on higher nervous activity is of great philosophical significance since it provides a basis in science for the theory of reflection evolved by Lenin. The development of Pavlov's theory was a heavy blow against idealism. Foreseeing a hostile reaction to his work from idealists, he wrote in 1906, that "in dealing with the highest vital phenomena, the fact must not be overlooked, that a systematic appreciation of natural science to the last limits of life will not be able to avoid misconception and opposition from those who are accustomed to regard these phenomena from another point of view and are convinced that this point of view is unassailable". (*Lectures on Conditioned Reflexes*, New York, 1928, p. 81).

As well as these achievements in synthetic study of vital phenomena, major advances are being currently made in research into physiological processes. Not only organs and tissues, but individual cells and even cell structures (nuclei, mitochondria, single nerve fibres) have become the objects of physiological and biochemical

examination. A branch of science, *microphysiology*, has developed, concerned on the one hand with micro-objects, and on the other hand with processes occurring in micro-intervals (i. e. within periods of thousandths of a second or shorter) and expressed in very small quantitative measures. The measurement of these processes, minute in size and short in duration, became possible through the use of advanced physics, electronics, and inorganic and organic chemistry.

Processes of intermediate metabolism, i. e. processes associated with the successive conversion of different chemical compounds in cells, tissues, and organs, have been studied in detail in this century. From investigation of the chemical statistics scientists proceeded to the examination of chemical dynamics. The method of labelled atoms, i. e. the introduction of substances containing radioactive or heavy isotopes into the organism, has proved of great value for that purpose. The presence of an isotope in a compound serves to "label" it, and allows us to follow its chemical conversions in the organism. Methods of microchemical analysis have also found wide use for revealing traces of certain substances in tissues and their extracts, especially the techniques of electrophoresis and chromatography.

Through research into the chemical dynamics of the organism, we have been able to establish the connection between various chemical processes and functional changes and physiological activity, which has given rise to a field called *chemical physiology* or *functional biochemistry*. A major achievement in this field has been the clarification of the chemical dynamics of muscular contraction and discovery of the source of the energy utilized during the work of the muscles (Meyerhof, Parnas, Lundsgaard). It was found that when a molecule of phosphoric acid splits off from certain organic compounds containing its radical (adenosine triphosphate and creatine phosphate) a great amount of energy is liberated, which is used up during muscular work. Physiologists and biochemists have come close to an explanation of the nature of muscular contraction; it has been shown (Engelhardt and Ljubimova, Szent-Györgyi, and others) that alterations in the colloido-chemical properties and physico-chemical state of muscle proteins (myosin and actomyosin) are accompanied by the liberation of mechanical energy, i. e. by the performance of external work, and that myosin, the protein responsible for muscular contraction, possesses enzymatic properties and catalyses the splitting off of one molecule of phosphoric acid from adenosine triphosphoric acid.

The development of research in the field of chemical physiology in this century has been marked by the formation of new branches, endocrinology, vitaminology, and the study of mediators.

*Endocrinology* is concerned with the physiology, biochemistry, and pathology of the endocrine glands, which produce and secrete

hormones, chemical substances of high physiological activity, into the blood, i. e. substances minute quantities of which are capable of causing sharp changes in the condition and activity of many body organs. Clinical physicians who linked the development of certain diseases with pathology of the endocrine glands were the first to consider their function. Only much later, at the end of the last century, did Brown-Séquard and then other physiologists of this century demonstrate that the endocrine glands, for example, the gonads, the suprarenal glands (adrenals), the pancreas, the thyroid, the parathyroids, and the pituitary body (hypophysis) produce highly active substances. The detailed experimental study of endocrine functions is an achievement of our century, and great advances have been made in this field. The chemical composition of many hormones has been established and their mode of action recognized; some of them have been synthesized in the laboratory. It has been shown that certain diseases occur as the result of deficient production of hormones by one gland or another, and others as the result of their excess; effective methods of treatment of many diseases of the endocrine glands have been elaborated on the basis of physiological data.

The study of vitamins, *vitaminology*, is concerned with research into the special group of substances in food that are necessary for control of the processes of metabolism and growth, and that are neither proteins, fats, carbohydrates, nor mineral salts, and do not serve as sources of energy. Vitamins were discovered in 1880 by Lunin, but their thorough study was only begun between 1910 and 1912. The term *vitamins* was proposed by the Polish scientist Cazimir Funk. This new field attracted the attention of physiologists, biochemists, synthetic chemists, pathologists, and representatives of various clinical specialities. About thirty vitamins are now known; in many cases their chemical structure and mode of action have been determined and methods of purification and chemical synthesis have been worked out for most of them. It was established that they are indispensable to the normal course of metabolism and that some form active groups of enzymes. The daily vitamin requirements of people of different age and occupation have been determined, and astonishing advances have been made in the diagnosis, treatment, and prevention of diseases due to the absence or deficiency of vitamins in food.

The *study of mediators* is concerned with the investigation of the role of certain chemical compounds formed in the nerve endings, which are chemical transmitters of nerve impulses, conveying them from the nerve ending to the cells of peripheral organs or to nerve cells. They were discovered in 1920 by Loewi in experiments on stimulating the nerves of an isolated frog heart. His discovery was confirmed and advanced by many scientists (Samoilov, Kibyakov,

and others in the USSR, Cannon and Nachmansohn in the USA, H. Dale and Feldberg in England, Bacq in Belgium, Minz in France). The formation of physiologically active substances through excitation and inhibition of all parts of the central and peripheral nervous systems has now been demonstrated. The group of mediators was found to include acetylcholine, adrenaline, and its derivative noradrenaline, and certain other substances; their mode of action is now being intensely studied. It has been shown that their importance is not limited to their role as transmitters of nerve impulses in the nerve endings, but that they are also factors altering the excitability and physiological state of nerve tissue. Studies of mediators have yielded results of great practical importance to the clinic. Their production, action, and decomposition have been found to be impaired in a number of diseases of the nervous system and with certain intoxications, and new measures for treatment of these conditions have been recommended and introduced into medical practice.

Through the achievements of endocrinology, vitaminology, and the study of mediators, the extremely important role of certain chemical compounds in the control of vital activity has been revealed. Chemical factors are involved in effecting the co-ordination, and control of functions. The effect exerted on body functions by substances produced in one group of cells and tissues, and carried by the blood and tissue fluid to other cells and tissues, is designated by the term *humoral control* (Latin *humor* moisture, fluid). It would be wrong, however, to conclude that it is a special control system independent of the nervous system. The production and action of humoral, chemical factors in the organism is controlled by the nervous system; humoral control mechanisms are governed by the nervous mechanism which is the highest form of co-ordination and regulation of functions in the whole organism. The formation of humoral factors and their action are a link in the single chain of neuro-humoral control of functions, in the study of which Soviet researchers like Orbeli, Bykov, and Stern, have taken an active part.

The physical trend in research also greatly enriched physiology, above all the advances in electrophysiology in most part due to the utilization of electronics and radio techniques. The introduction of the string galvanometer (Einthoven, Samoilov) at the beginning of the century and then the use of electron amplifiers of electric current, or voltage, and oscillographs (Gasser, Adrian) made possible detailed analysis of the electrical phenomena in the central and peripheral nervous systems, the heart, and the muscles.

The importance of these studies is that the electrical changes, the so-called action currents or potentials, are inherent to the excitation process. Electrophysiological research has received wide application in medical practice. Thus, *electrocardiography*, the recording of the electrical manifestations of cardiac activity, has

proved a sensitive diagnostic method detecting disorders of cardiac performance in diseases of the heart. The recording of electrical manifestations of cerebral activity, *electroencephalography*, proves valuable in diagnosing certain diseases of the brain, particularly in localizing brain tumours.

In this century, too, physiologists began employing the theories and methods of physical chemistry developed at the end of the previous century. The first attempts were made by Chagovets (1896-1903), and then by the American biologist Loeb, by the German physiologist Bernstein and chemist Nernst and by the Russian physicist and physiologist Lazarev. Chagovets applied Arrhenius' theory of electrolytic dissociation to establish the nature of the electrical phenomena in living tissues and concluded that bio-electrical potentials are due to differences in the tissue electrolyte concentration. Later he advanced the idea that alterations in the ion concentration of the stimulated area are the basis for the excitation of a nerve. His concepts were widely accepted and were the foundation for the current hypotheses on the nature of the nervous process and of the electrical manifestations of excitation (Hodgkin, Huxley).

In the twenties and thirties of this century it was found that the conduction of impulses along nerve fibres was attended by an increase in oxygen expenditure and formation of carbon dioxide, which provided evidence that oxidation processes were intensified in an excited nerve. Later Hill's modification of the thermoelectrical method of measurement made it possible to establish the production of heat in a nerve during and after conduction of an excitation wave. These experiments led to the important conclusion that the conduction of nerve impulses is a complex process whose initial stage is the rise of an action current owing to the movement of ions through the fibre membrane; it is followed by complex biochemical processes associated with intensification of energy metabolism, as the result of which the ion concentration on both sides of the membrane is restored, and the nerve fibre again becomes capable of conducting an impulse (Ukhtomsky).

Much progress has also been made in study of the functions and regulation of the internal organs; the principles of cardiac activity have been analysed in detail (Starling and Lewis in England, Samoilov and Focht in Russia, Wiggers in the USA), and penetrating study was made of vascular reactions (Hering in Germany, Heymans in Belgium, Parin and Chernigovsky in the USSR), capillary circulation (Krogh in Denmark), mechanisms of respiration and the transport of gases by the blood (Verigo in Russia, Barcroft and Haldane in England, Van Slyke in the USA, Kreps in the USSR), the chemism, mechanism, and control of digestive processes (Pavlov, London, Babkin, Razenkov, Bykov, Bayliss, Ivy, and others), and the principles of renal function (Cushny, Richards,

Ginetsinsky, and others). Study of the vegetative nervous system, i. e. of the part of the nervous system that supplies the internal organs, blood vessels, and sweat glands, and that participates in the control of metabolism in all body tissues, has been elaborated in the works of Gaskell, Langley, Cannon, Mislavsky, Orbeli, and others.

A great contribution has been made in this century to study of the physiology of the lower parts of the central nervous system; study of the nerve centres has been developed, and the general principles of the co-ordination of functions and the peculiar course of reflex reactions in the spinal cord, medulla oblongata, mid-brain, cerebellum, and subcortical nuclei, have been investigated (research by Sherrington in England, Magnus in Holland, Vvedensky, Ukhtomsky, Beritashvili, Asratyan in the USSR, Dusser de Barenna, Fulton in the USA, Eccles in Australia, and others). The functions of the reticular formation of the brain have been unravelled (Magoun and Moruzzi, Anokhin, and others).

The many new facts and theoretical postulates obtained in the fields of comparative physiology, and the physiology of aging have made it possible to pose the problem of the way functions have evolved and to form a new branch of science, *evolutionary physiology* (Orbeli, Koshtoyants, and others).

The twentieth century has witnessed an immense growth of research and of the numbers of physiologists working on physiological problems in different countries. In 1889, for instance, little more than seven hundred works on physiology and related disciplines were published; in recent years the annual number of publications in these fields has exceeded thirty thousand.

The organization of research has also changed in our time. Problems are mainly studied in large scientific institutes and laboratories equipped with complex instruments, and whose staffs include biophysicists, biochemists, morphologists, mathematicians, and engineers working together with physiologists.

## Chapter 2

# GENERAL PRINCIPLES AND BASIC CONCEPTIONS OF PHYSIOLOGY

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### FUNCTIONS OF THE ORGANISM

Physiology deals with the functions of the living organism and its parts; definition of the terms "organism" and "function", therefore, is an essential preliminary to its exposition.

#### THE ORGANISM

An *organism* is an independently existing unit of the organic world, a self-regulating system that reacts as a single whole to various changes in its environment. It can live only in constant mutual interaction with the medium surrounding it, and restores itself by that interaction. The existence of an organism is impossible, as Sechenov stressed, without the presence of an environment sustaining it.

Every organism has a definite organizational structure. In viruses, the lowest living organisms, there is only organization of molecules of the protein and nucleic acids of which they are formed. This can be considered the *molecular level of the organization*. More highly organized unicellular organisms, like *Paramecium*, have a more complex structure: a nucleus, mitochondria, superficial and intraprotoplasmic membranes, and vacuoles are distinguished. Here we have a supermolecular, *cellular level of organization* attended by a certain differentiation in functions of the various intracellular structures. Thus, intracellular contractile fibrils, flagellae, and cilia

perform the function of movement, the functions of digestion and excretion are carried out in some cells by the vacuoles, and so on.

In the course of evolutionary development, differentiation of cells has occurred in multicellular organisms, i. e. differences in size, shape, structure, and function developed. Identically differentiated cells form tissues characteristic features of which are a common structure, morphology and function, and interaction. Various tissues are specialized in function, that is, are adapted to accomplish different processes of vital activity. Thus, muscular tissue is specialized in motor function and contractility is its characteristic property; the cells of the gland tissue elaborate and excrete certain chemical compounds (hormones, enzymes, etc). While adapted to perform a definite type of activity, the highly differentiated tissue cells at the same time have functions common to all cells, namely, metabolism, nutrition, respiration, and excretion. The interaction of the cells forming a tissue, and the complex structure and specialized function of the tissue that give them their morphological and functional peculiarities, are grounds for distinguishing a *tissue level of organization* of living organisms.

Organs composed of different tissues originate at a definite stage of the development of species and individual organisms. Organs are anatomical formations with their own peculiar structural and functional union of different tissues. They are working apparatus of an organism, specialized to perform complex functions necessary for its existence as a whole. For example, the heart serves as a pump to force blood from the veins into the arteries, the kidneys excrete the final products of metabolism from the body and maintain a constant concentration of electrolyte in the blood; bone marrow has the function of blood formation, and so on.

The presence in organisms of organs differing in structure and function allows us to speak of an *organ level* of organization.

The complex of organs that participate in any of the complicated processes of activity form anatomical or functional units or systems of organs. These include the nervous and endocrine systems which control the functioning of all the organs of the body, and the systems of the organs of locomotion (movement in space), respiration, blood formation, digestion, excretion, and reproduction. Of all these systems, the nervous system is the most important one for the organism as a whole, uniting and regulating the condition and activity of all the other systems and determining the organism's behaviour in its environment. The presence of systems of organs, each specialized to perform some type of activity for the organism as a whole, determines the *system level* of the organization.

Each of the levels of the organization of living organisms enumerated is characterized by its own distinctive physiological regularities, peculiar to itself, which cannot be understood solely by studying

the other levels. To explain the processes occurring at the different levels requires various methods of approach and different instrumental techniques. It needs to be stressed that to understand the functions of higher organisms it is necessary to study all their levels of organization — molecular, cellular, tissue, organ, and system, and to synthesize all the information obtained about them by researchers, since the living organism, in possessing a complex organization, is an integrated whole in which the function of all its structures, cells, tissues, organs, and systems is co-ordinated and to which they are subordinated.

#### PHYSIOLOGICAL FUNCTIONS

*Physiological functions* are manifestations of vital activity of an adaptational nature. While performing various functions, the organism adapts itself to its environment or adjusts the environment to its requirements.

Any physiological function of a cell, tissue, organ, or organism as a whole, is the result of the whole history of the species and of the individual development of living creatures — i. e. of their phylogeny and ontogeny. The definite functions of living structures arise during this development and undergo both qualitative and quantitative changes. For that reason, study of the origin and development of each separate function is an important aspect of physiology.

The principal function of a living organism is the *exchange of matter and energy*, a complex of chemical and physical changes, and of transformations of matter and energy, taking place constantly and continuously in the organism and in all its structures.

That exchange, or *metabolism*, is an essential condition of life. It distinguishes living matter from non-living, the world of living organisms from the inorganic world. Changes in substances and the transformation of energy also occur in the inorganic world, but these processes differ in principle between the living organism and non-living matter. The essence of this difference was beautifully formulated by Friedrich Engels in the *Dialectics of Nature*: "Such metabolism can also occur in the case of inorganic bodies and in the long run it occurs everywhere, since chemical reactions take place, even if extremely slowly, everywhere. The difference, however, is that inorganic bodies are destroyed by this metabolism, while in organic bodies it is the necessary condition for their existence." (London, 1940, p. 196). Life is possible only with a metabolism that supports the existence of living protoplasm and involves its self-renewal. Arrest of its processes results in death, destruction of the protoplasm, and irreversible breakdown of its chemical compounds, primarily of its proteins.

All other physiological functions, whether growth, development, reproduction, nutrition and digestion, respiration, secretion and

excretion of the products of vital activity, movement, reactions to environmental changes, etc., are associated with metabolism. A definite complex of transformation of matter and energy underlies every physiological function, and that is equally true of the functions of separate cells, tissues, or organs, and of the organism as a whole.

The performance of any function is attended by structural changes due to physico-chemical processes and chemical transformations in the cells of the organism. In some cases they may be seen under the microscope, and valuable data have been obtained that way employing cytochemical and histochemical methods the essence of which is to use special reagents to identify the localization of certain substances in the cells and tissues and the changes they undergo during various functions. In other cases the changes in the cellular structure cannot be detected through the optical microscope because they are often submicroscopic, i. e. they occur beyond its limits of visualization. They can, however, be established by the electron microscope which has a higher power of resolution and magnification (magnifying the image 100,000 to 200,000 times). Electron microscopy has made it possible to determine the submicroscopical changes occurring in a muscle cell when it contracts, and in a nerve ending during the transmission of a nerve impulse to an innervated organ. Histochemical and electron microscopy studies have confirmed the assumption that every physiological function is inseparably associated with structural changes in the cells. Those changes, as a rule, are reversible, the initial state being rapidly restored. Only in separate instances may they be irreversible. For example, there are two types of secretion, i. e. excretion of various substances by a cell: in one type the cell remains intact although it discharges a certain product, in the other, part of the cell is destroyed or the whole cell itself.

To understand the nature of the processes underlying the various functions of an organism, and of its organs and cells, it is important to study the minute changes in the exchange of matter and energy occurring in very short intervals of time (within milliseconds or even microseconds). That is because many of the most important functions of cells are associated with such quantitatively insignificant processes, and for that reason, the working out of even more sensitive and precise methods of research that will enable us to determine and measure very small and rapidly occurring physical and chemical processes is of extraordinary importance for physiology. Much that is new has been gained in that respect by use of the latest advances in physics, chemistry, and engineering which have supplied scientists with new methods of research. Thus, the heightened sensitivity of electrical methods of measuring temperature has made it possible to determine heat production in a nerve fibre during the transmission of a single nerve impulse, when

the temperature rises only by  $2 \cdot 10^{-6}^{\circ}\text{C}$  (i. e. by two millionths of a degree). This has shown that the transmission of a nerve impulse is attended with an intensification of metabolism, even if insignificant. The use of electron amplifiers and oscillographs has made it possible to detect differences in electric potential of one microvolt between nerve fibres and their endings, and that in turn has revealed the mechanism of the influence of certain nerves on the tissues of the organism. New chemical techniques enable us to ascertain the structure of many of the chemical compounds that are formed in the body in small amounts and that have an effect on it in concentrations of  $1 \cdot 10^{-8}$ , and that has contributed to deeper understanding of chemical interaction of cells and tissues in the body.

Though manifested as chemical and physical (including mechanical) changes, the functions of an organism cannot be ascribed to single one of them, since life functions are a complicated, mutually connected aggregate, a unity of all those processes. In studying any living object, whether a separate cell, or a complex, highly-organized organism, the physiologist is obliged to synthesize the data of physical, chemical, and morphological research, because the body is the "higher unity which within itself unites mechanics, physics, and chemistry into a whole." (Engels, *op. cit.*, p. 267).

#### THE ORGANISM AND ITS ENVIRONMENT

Any organism, whether unicellular or multicellular, requires definite conditions for its existence, that are provided by the habitat to which its species has adapted itself in the course of its evolution. An organism functions normally only when its environment provides it with the possibility to obtain the nutrients necessary to replenish substances and energy expended and when it exists in the medium (water or air) necessary to it, at a definite temperature, barometric pressure, intensity and spectrum of light, etc.

The types of adaptation of different organisms to all the environmental factors enumerated and their interrelation with that environment are extremely diverse. For example, animal organisms need organic nutrients and have not the capacity to synthesize complex organic compounds from inorganic matter. On the contrary, green plants accomplish that synthesis during a most important biological process, *photosynthesis*. This difference in the relations of animals and plants to their environment ensures the cycle of matter in living nature.

Plant organisms utilize inorganic nitrogenous compounds (ammonia and saltpetre) derived from the soil by their root system, and synthesize nitrogen-containing protein substances. Animal organisms cannot synthesize proteins from inorganic nitrogenous compounds; their cells only produce protein from amino acids obtained from their food. As a result of deamination and decarbo-

xylation during vital activity, there is a constant breaking down of amino acids with the formation of simpler nitrogenous compounds (ammonia, urea, etc.) which are again utilized by plants and certain micro-organisms for the synthesis of proteins.

The cells of most animals are *aerobes*, i. e. they require molecular oxygen, entering the organism from the environment, to oxidize organic substances to  $\text{CO}_2$  and water. On the other hand, some organisms are *anaerobes*; they have no need of free oxygen which is not only not useful to them but even harmful. They obtain the energy they require to live from anaerobic breaking down (i. e. without oxygen) of nutrients.

The relationships of various organisms to temperature, barometric pressure, humidity, and the amount of electrolytes in a water medium are extremely diverse. Thus, some animals can live only in the fresh water of lakes and rivers with a salt content less than 0.1 per cent; others can live only in salt water containing about 3 per cent of electrolytes.

Various changes in the environment exert a powerful influence on physiological functions: e. g. changes in the amount and composition of nutrients; changes in the composition of the air and in its content of oxygen and carbon dioxide and in the composition and concentration of the electrolytes in water; alterations of temperature and barometric pressure and in the spectrum and intensity of light; the presence of toxic substances in the medium of radioactive radiation, etc. Some factors have a favourable effect on the functions, while others inhibit them and are fatal to the organism.

The vital activities of organisms normally take place only with definite environmental conditions and the limits within which these conditions may vary are relatively small, i. e. must be relatively constant. It should, however, be borne in mind that the limits of fluctuation tolerated by the organisms of higher animals are much wider than those required for the normal functioning of most of their cells for the reason that the habitat of the cells is the internal *environment* of the organism, which changes much less than its external environment. The *internal environment* is the blood, lymph, and tissue fluid surrounding the organism's cells.

## HOMEOSTASIS

The organisms of higher animals have developed adaptations that counteract many of the influences of the external environment and provide relatively stable conditions of existence for the cells. This has the greatest importance for its vital activity as a whole. The following are some examples. The cells of the organisms of warm-blooded animals, i. e. animals with a constant body temperature, normally only function within narrow temperature limits

(36° to 38°C in human beings). Temperature changes beyond these limits lead to disturbances in the vital activity of the cells. At the same time, the organisms of warm-blooded animals can normally exist within much wider fluctuations of temperature in the external environment; the polar bear, for instance, can live at temperatures between – 70°C and +20° or +30°C. That is due to the regulation of heat exchange between the organism as a whole and its surroundings, i. e. regulation of heat production (the intensity of chemical processes accompanied by the liberation of heat) and heat emission. With a low temperature in the external environment, heat production is increased and heat emission is reduced, so that body temperature is kept constant during fluctuations of the surrounding temperature (within certain limits).

The cells of an organism function normally only under a relatively stable osmotic pressure conditioned by a constant content of electrolytes and water in them. An increase or decrease in osmotic pressure gives rise to severe functional and structural disturbances in the cells, but the organism as a whole can live for some time either when given an excess amount of water or when deprived of it, and when it gets large or small amounts of salt in its food. The explanation is the presence of adaptational mechanisms in the organism that facilitate maintenance of a constant amount of water and electrolytes in the body. With abundant intake of water large amounts are expelled by excretory organs (kidneys, sweat glands, skin), while with a deficiency water is retained in the body. The excretory organs control electrolyte content in the same manner, eliminating excess rapidly, or retaining them in the body fluids as when the supply of salts is deficient.

The concentration of individual electrolytes differs in the blood and tissue fluid, on the one hand, and in the cell protoplasm on the other. Blood and tissue fluid contain more sodium ions, while cell protoplasm has more potassium ions. The difference in ion concentration inside and outside of the cell is achieved by a special mechanism that retains potassium ions within the cell and prevents an accumulation of sodium ions there. This mechanism, the nature of which is not yet clear, is known as the sodium-potassium pump, and is associated with cell metabolism.

The cells of an organism are extremely sensitive to changes in the concentration of hydrogen ions and an increase or decrease in their concentration severely impairs cellular vital activity. A stable concentration of hydrogen ions is characteristic of the internal environment and depends on the existence in the blood and tissue fluid of a “buffer system” (see p. 58), and on the activity of the excretory organs. Acids and alkalies are rapidly excreted from the body when their content in the blood rises, and in this way a constant concentration of hydrogen ions is maintained in the internal environment.

Cells, nerve cells in particular, are very sensitive to changes in blood sugar level, sugar being an important nutrient. Stability of the blood sugar level is therefore of great significance to life processes. With a rise of sugar level in the blood, a polysaccharide *glycogen* is synthesized from it and stored by the cells of the liver and muscles. A fall in blood sugar level leads to the breaking down of the stored glycogen with the formation of glucose which passes into the blood.

Stability of the chemical composition and physico-chemical properties of the internal environment is a most important feature of the organism of higher animals. Cannon proposed to call this state as *homeostasis*, a term now widely used. Homeostasis is expressed by a number of *biological constants*, i. e. stable quantitative indices characteristic of the normal state of the organism. They include the values of body temperature, the osmotic pressure of blood and tissue fluid, their content of sodium, potassium, calcium, chlorine, and phosphorus ions, and of protein and sugar, the concentration of hydrogen ions, and a number of other indices.

In noting the stability of the composition, physico-chemical, and biological properties of the internal environment, it must be stressed that this state is not absolute, but is relative and dynamic, and is achieved by the continuous work of a number of organs and tissues that regulate variations in the composition and physico-chemical properties of the internal medium occurring as a result of the organism's own vital activity and under the influence of changes in the external environment.

The various organs and systems have different roles in maintaining homeostasis. Thus, the organs of the digestive system supply the blood with nutrients in the form in which they can be utilized by body cells. The organs of the circulatory system cause a constant flow of blood transporting various substances around the organism, as a result of which nutrients, oxygen, and various chemicals formed in the body are supplied to the cells, while decomposition products, including carbon dioxide eliminated by the cells, are carried to the organs that excrete them. The respiratory organs provide the blood with oxygen and eliminate carbon dioxide from the body. Considerable chemical transformations take place in the liver and other organs, as the synthesis and breaking down of many chemical compounds of significance for cell activity. The excretory organs, i. e. the kidneys, lungs, sweat glands, and skin, eliminate from the body the end products of the decomposition of organic substance and maintain a constant level of water and electrolyte in the blood and, consequently, in the tissue fluid and cells.

The nervous system has a most important role in maintaining homeostasis. Reacting sensitively to changes in both the external and the internal environment, it regulates the activity of organs and systems by preventing or balancing shifts and disturbances already occurring or that may have occurred in the organism.

Owing to the development of the mechanisms that ensure relative stability of the internal environment, the cells of the organism are less affected by the variable external influences. As Claude Bernard put it, uniformity of the internal medium is a prerequisite of a free and independent life.

Homeostasis has definite limits. It is disturbed by exposure, particularly lengthy exposure of the organism to conditions differing greatly from those to which it is adapted, and shifts incompatible with normal life may occur. Thus, with a significant raising or lowering of the external temperature, body temperature may rise or fall, and a fatal over-heating or cooling of the body result. Likewise, a significant limitation of the supply of water and salts to the organism, or complete deprivation of them, will disrupt the relative stability of the composition and physico-chemical properties of the internal environment after a time, and end its life.

A high level of homeostasis occurs only at certain stages of the development of species and individuals. The lower animals do not have sufficiently developed adaptative mechanisms to cushion or eliminate the influence of changes in the external environment. A relatively constant body temperature (*homiothermy*), for example, is maintained only in warm-blooded animals. The body temperature of the so-called cold-blooded animals is closer to that of the environment and is variable (*poikilothermy*). The body temperature and the composition and properties of the internal environment in new-born animals are not as constant as in adults.

Even slight disturbances of homeostasis give rise to a pathological condition, so that determination of such relatively constant physiological indices as body temperature, arterial pressure, the composition and physico-chemical and biological properties of the blood, etc., are of great diagnostic value.

#### EXCHANGE OF MATTER AND ENERGY AS THE PRINCIPAL FUNCTION OF THE ORGANISM

The phenomena of metabolism include the taking in of various substances by the organism from the external environment, their assimilation and transformation, and the elimination of the breakdown products of decomposition. All these processes of transformation are attended by a multiplicity of various chemical, mechanical, thermal, and electrical phenomena, and by a continuous transformation of energy; the potential energy of complex organic compounds is liberated through their breakdown and is transformed into heat, mechanical power and electricity. Thermal and mechanical energy are released in the main. The release of electrical energy is quantitatively low but it is of very great physiological importance for the functioning of the nervous system. In some organisms potential chemical energy may also be transformed into light.

The energy released in the organism is utilized not only to maintain body temperature and perform external work, but also to sustain the structure and life of the cells, and the processes associated with their growth and development.

Animal organisms continuously use up various substances which are broken down within them and a considerable amount of energy, and therefore require food containing complex organic compounds that can be used as sources of plastic material and energy.

Metabolism and the transformation of energy are inseparable. Matter cannot undergo changes without transformation of energy, and there is no exchange of energy without exchange of matter. Production of heat is the quantitatively predominant result of the energy processes occurring in the organism. Determination of the thermal energy released in an organism and converted into units of heat or the mechanical energy of external work can be used as a means of quantitatively expressing its energy consumption, and as an index of the intensity of its metabolism. Modern physiology widely uses the data of power engineering and the theoretical principles and methods of research of thermodynamics to study biological processes. This trend in research is possible because the processes of metabolism and energy exchange in a living organism conform with the greatest generalization of science, the law of the conservation of matter and energy.

Matter and energy are not formed in the living body and are not destroyed in it, but are simply transformed, absorbed, and eliminated.

This was first shown experimentally in 1781 by Lavoisier and Laplace. They determined the amount of heat given off by the body of a guinea pig in an ice calorimeter, and simultaneously studied the elimination of carbon dioxide which made it possible to calculate the quantity of carbon oxidized in the organism. They then measured the quantity of heat released during the combustion in a calorimeter of a quantity of coal corresponding to that amount of carbon. The values of both calorimetric findings were found to be identical. It was thus shown that the release of energy in an organism is the consequence of oxidation processes.

The conclusions of Lavoisier and Laplace have since been verified many times, each time with more perfected research techniques, and yielding results analogous in their theoretical significance. Particularly clear data were obtained by Rubner in experiments on dogs and by Atwater in studies of human beings. Although the experiment was extremely complicated, the researchers found that the values of the heat produced during the oxidation of nutrients in the organism and by their combustion outside of it were amazingly close.

## ASSIMILATION AND DISSIMILATION

Metabolism is the unity of two processes, assimilation and dissimilation.

*Assimilation* is the sum of the processes by which living matter is produced: the utilization by the cells of nutrients entering the organism from the external environment, the formation of complex chemical compounds from simpler ones and the synthesis of living protoplasm. The term is derived from the Latin *assimilare* meaning to make like, and defines the utilization of various substances by the cells resulting in their transformation into living matter.

*Dissimilation* (L. *dissimilare* to make different) is the disintegration of living matter, the decomposition and breakdown of the materials that form the cell structure, and of protein compounds in particular. The breakdown products are eliminated from the organism.

It is often difficult to decide whether certain biochemical processes are to be regarded as assimilation or as dissimilation, for example, the processes of transferring definite chemical groups (phosphate and amino group radicals) from one compound to another, i. e. the processes of transphosphorylation, transamination, etc.

Assimilation and dissimilation are mutually opposite and inseparably connected. Assimilation is accompanied by an intensification of dissimilation processes which in turn pave the way for processes of assimilation. The interconnection of the two can be illustrated by the many experiments that have shown that dissociation reactions become greatly intensified during the growth of organisms and cell multiplication, when vigorous formation of protoplasm and protein synthesis take place. Energy expenditure therefore increases sharply during growth. Warburg found that oxidation processes increase six-fold at the beginning of cell multiplication following the fertilization of sea urchin eggs. Similarly, processes of dissimilation are greatly intensified in the entire organism during rapid growth of a malignant tumour when there is intensive formation of new cells.

Although they are inseparably connected, the processes of assimilation and dissimilation are not always mutually balanced. Thus, while a significant intensification of both processes is observed during growth of an organism, there is a relative preponderance of assimilation.

## THE PHYSIOLOGICAL SIGNIFICANCE OF PROTEINS, NUCLEIC ACIDS, AND CERTAIN METABOLIC PROCESSES

There are differences between the chemical transformations occurring in the various organs, tissues, and cells of any one organism or of different species. Their physiological significance also differs. The processes of synthesis in the cells of various tissues and organs and in those of the different species, i. e. the formation of certain

chemical compounds essential for the cell and the organism as a whole, may either be common to all of them or be specific to only some of them.

The evolution of species and the individual development of organisms show not only in the morphological changes but also in biochemical ones (biochemical evolution) that underlie both the phylogenesis and the ontogenesis of functions. A definite trend in metabolic processes characterizes the processes of *morphogenesis*, i. e. the growth and development of the organism and the differentiation of its cells. The differences in the molecular and intramolecular physico-chemical processes occurring in the microstructures of the cell nucleus and protoplasm, and in their organelles, are inseparably connected with the features of their vital activity and functions.

Proteins and nucleic acids have the greatest biological significance in the life of cells and in their metabolism, and all the principal manifestations of life are associated with them.

Current research on the nucleic acids, which are constituents of the cell nucleus and protoplasm, has resulted in discoveries of outstanding scientific importance and has established the role of these substances in the synthesis of proteins and in the transmission of characteristics.

The nucleic acids of the nucleus (*deoxyribonucleic acid* or DNA) and of protoplasm (*ribonucleic acid* or RNA) are extremely complex macromolecules. They are polymers — polynucleotides made up of a great number of mononucleotides. One DNA molecule contains at least ten thousand mononucleotides. The structure of a mononucleotide molecule is formed of alternating radicals of phosphoric acid and a pentose pentacarbide sugar (deoxyribose in DNA and ribose in RNA). To the carbohydrate radicals are joined side chains of nitrogen-containing bases (adenine, guanine, cytosine, and thymine in DNA, and adenine, guanine, cytosine, and uracil in RNA). Various combinations of these four bases within the mononucleotide lead to numerous varieties in the structure of polynucleotides. X-ray structural studies (studies of X-ray diffraction) made by Crick and Watson revealed that DNA molecules are two elongated chains twisted around each other, forming a double helix. The structure of DNA is specific for any given species of living organism.

The molecular structure of DNA determines the structure of RNA, while the latter in turn determines the structure of the protein molecule synthesized in the cell protoplasm, i. e. the sequence of the amino acids making up the protein. The role of DNA has been compared to that of the architect who designs a building, and the role of RNA to that of the builder who constructs it from separate bricks.

Most biologists regard DNA as the carrier of genetic information, the substance whose structure determines the hereditary properties

of an organism. These characters are coded in the sequence in which the bases are arranged in the DNA molecule, which determines the hereditarily fixed features of protein and enzyme synthesis in the cells of the organs of a developing embryo.

This research brings nearer the time when it will be possible as Timiryazev and other outstanding biologists have dreamed to "model organic forms". The transformation of one bacterial strain into another, i. e. of one variety into another, by transferring the DNA of the one to the other, has already been achieved.

*Proteins* are very complex chemical compounds, polymers, formed from various combinations of twenty different amino acids. Protein synthesis occurs with the direct guidance of the nucleic acids which play the part of a template or matrix, serving as a "framework" for the "assemblage" of the protein molecule from separate amino acids. The various genetically conditioned combinations of the structural components of the nucleic acids determine the synthesis in the cell of the structurally varied proteins formed by different organisms and by their various organs and tissues.

There are differences between the proteins of animals of different species, between those of different individuals of the same species, and between those of the various organs and tissues of the same individual. For that reason, we distinguish the *specificity of cell proteins* for species, individuals, organs, and tissues. The fact that an organism does not tolerate the introduction into its blood of proteins derived from an animal of another species and displays various reactions (the formation of immune bodies, anaphylactic reactions, etc., see p. 81) is associated with species specificity. The introduction of natural, i. e. untreated, heterogenous proteins often causes severe, and even fatal, disturbances in the state of an organism. That is why animal blood or plasma cannot be transfused to a human being. Transplants of organs from animals of one species to another are unsuccessful owing to this biological incompatibility of proteins. With the operations known as *heterotransplantation* or *heteroplasty*, the transplanted organ does not survive and dies within a short time. The individual specificity of the proteins of different organisms of one and the same species is less manifest; nonetheless, it is precisely with that, that the failure of transplants from an animal to another of the same species is associated. These operations, known as *homotransplantations* or *homoplasty*, also usually terminate in the resolution or death of the transplant.

The organ and tissue specificity of proteins finds expression in differences between proteins of the various organs and tissues. Thus, highly differentiated cells adapted to the performance of definite functions contain proteins characteristic of, or specific to, just those cells, e. g. the proteins forming specialized cell structures, like myofibrils, the fine slender threads within muscle cells, that contain the proteins actin and myosin which possess certain enzyme properties and are

responsible for the contraction of the muscles (for which reason they are called contractile proteins). The cells of connective tissue contain collagens, which form the protein framework of the fibres composed of these cells. Collagen fibres are marked by flexibility, tensile strength, and a high modulus of elasticity, properties associated with the supporting and mechanical functions of the cells of connective tissue (whether loose and fibrous or cartilaginous and bony).

Many proteins are important because of their enzyme properties, i. e. their capacity to produce a catalytic action on certain processes of breaking down and building up various organic compounds.

The continuous breaking down and resynthesis of cell proteins resulting in their constant self-renewal is a feature of the protein metabolism occurring in the cells of organisms.

The synthesis of the proteins of protoplasm and cell structures is one of the group of *plastic processes* associated with the building up of cells and intracellular formations. These processes are distinguished from the *energy processes*, whose main importance is in supplying cells with the energy necessary for their activity. An energy process of particular importance is the metabolism of certain substances whose decomposition is the main source of the energy, i. e. utilized for cell functions like muscular contraction and many processes of synthesis. These substances include *energy-rich compounds* like *adenosine triphosphate* (ATP). A great quantity of energy is released when two phosphate radicals split off from ATP (the splitting off of one radical releases about 10,000 calories per grammemolecule of matter).

There are a host of chemical transformations that are specific for various cells. Thus, some compounds are formed only in certain cells or intra-cellular structures, and their formation and excretion into the external or internal environment constitute the main function of the cell. The production and excretion of hydrochloric acid, for example, are characteristic only of the delomorphous cells of the gastric glands; the enzyme trypsinogen is produced only in the cells of the pancreas concerned with external secretion. The synthesis of insulin, which plays a very important role in carbohydrate metabolism, also takes place in the pancreas, but only in cells concerned with internal secretion and known as the beta cells of the insular tissue. Acetylcholine, the chemical transmitter of a nerve impulse from the nerve ending to the innervated organ, is formed in a certain part of the nerve ending.

Metabolic processes, i. e. the synthesis and breaking down of compounds, differ in character not only within different cells but also within the various structures of highly differentiated cells. The part played by these cell structures in metabolism has been established by means of histochemical methods and tracer techniques. The breaking down of carbohydrates, glycolysis, was found to

occur in the cytoplasm, and oxidizing phosphorylation in the mitochondria; the early stages of protein synthesis occur in the cytoplasm, but the later stages in the microsomes. Similarly, there are differences in the distribution of the different enzymes in the various parts of the cells.

The continuous metabolic processes taking place in the cell like all other forms of physiological function, are not constant and unchangeable, but are dynamical and variable. Metabolism may be intensified or reduced, and may change qualitatively under the influence of the external environment and alterations in the organism's internal environment. This occurs always with cell activity, when metabolism of rest (any state of rest in an organism is relative because vital activity is characterized by expenditure of matter and energy) changes into the metabolism of work, the latter increasing with intensification of cell activity.

#### BIOLOGICAL REACTIONS

Every living organism and all its cells possess irritability, i. e. have the property of responding to the effects of the external environment, or to disturbances of their condition by changes in their structure, by initiation, intensification or reduction of their activity, which is inseparably linked with quantitative and qualitative changes in metabolism and energy exchange. Changes in the structure and function of an organism and its cells in response to various influences are known as *biological reactions*, and the acts or influences that cause them as *stimuli*.

The term biological reaction has a very wide meaning, denoting all the forms of response of the organism and its tissues and cells to various influences.

Cell reactions are manifested in changes of the shape, structure, growth, and cell-division, by the formation of various chemical compounds within it, by the transformation of potential energy into kinetic (electrical, mechanical, thermal, and light), and by the performance of some kind of work (movement in space, elimination of substances, or osmotic activity to concentrate certain electrolytes).

The reactions of the organism as a whole, and all the complex acts of its behaviour in particular, are extremely diverse. Their performance is attended by changes in the activity of many organs and a vast number of cells, since the organism always reacts as a whole, as a single complex system, to various stimuli. Its reactions therefore cannot be regarded as the reactions of separate cells, although they are caused by cell activity, which reflects the general rule that the laws governing a system cannot be reduced to those governing the separate elements forming it.

## STIMULATION

Any change in the external environment or in the internal state of an organism can serve as a *stimulus* to the living cell or to the organism as a whole, if it is *sufficiently strong*, if it has developed *sufficiently rapidly*, and if it acts for a *sufficient length of time*.

The whole infinite variety of stimuli acting on cells and tissues can be divided into three groups: viz. physical, physico-chemical, and chemical. *Physical stimuli* are thermal, mechanical (a blow, pressure, puncture, spatial movement, acceleration, etc.), electrical, light, and sound. *Physico-chemical stimuli* are changes in osmotic pressure, in the ion concentration of the medium, and in the electrolyte composition of the colloidal state. *Chemical stimuli* include numerous substances that differ in composition and properties and which cause changes in cell metabolism or structure. Foodstuffs, drugs, and poisons entering the organism from the external environment, and many chemical compounds formed within it, like hormones and products of metabolism, are chemical stimuli capable of producing physiological reactions.

Stimuli affecting cells and causing their activity, that are of special importance to vital processes, are *nerve impulses*. Being natural, i. e. arising in the organism itself, electrical and chemical cell stimuli, passing either from the nerve endings to the central nervous system along the nerve fibres, or from the central nervous system to peripheral organs (muscles and glands), they cause changes in their condition and function.

According to their physiological significance stimuli are either adequate or inadequate.

*Adequate stimuli* are those that act upon a given biological structure in natural conditions, and to which that structure is specially adapted and extremely sensitive. The rays of the visible part of the solar spectrum are the adequate stimulus of the retinal rods and cones; pressure is an adequate stimulus of the tactile skin receptors, and various chemical substances of the taste buds of the tongue, while nerve impulses passing along the motor nerves to the skeletal muscles are adequate stimuli of them.

*Inadequate stimuli* are those to which a given cell or organ is not specially adapted. For example, muscular contraction is caused not only by adequate stimulus, i. e. impulses conducted along the motor nerve, but also by stimuli to which the muscle is not exposed in natural conditions; a muscle contracts in response to the effect of acids or alkalis, to sudden strain or a mechanical blow, to rapid heating, etc.

Cells are much more sensitive to their adequate stimuli than to inadequate ones, which is an expression of functional adaptation acquired in the process of evolution.

Various stimuli are widely used in physiological experiments to study the activity of cells, organs, and tissues, particularly the function of nerve cells and of the nervous system as a whole. *Electrical stimulation* is the most suitable for these purposes. It is advantageous because the intensity of the current used causes no detectable injury to living tissues: the effect of the current begins and ends very rapidly, and can be easily switched on and off, while that of chemical and thermal stimuli lasts longer. In addition, the dosage of electrical stimulation is easily regulated in intensity, duration, and rhythm.

Physiological experiments usually employ either direct stimulation, applied directly to the tissue under test (a muscle or a gland), or indirect, applied to the nerve fibres that innervate the given organ. By stimulating the fibres one can reveal the manner in which they act upon the organ. The reactions of the nervous system are studied by stimulating the receiving nerve endings (*receptors*) or nerve fibres passing to the central nervous system.

#### EXCITABILITY

Some cells and tissues (nerve, muscular, and glandular) are specially adapted to react rapidly to a stimulus, and are said to be *excitable*, while their capacity to respond to stimulation is known as *excitability*.

The measure of excitability is the *minimum strength of stimulus* that produces excitation, and is known as the *threshold of stimulation*. The higher the minimum strength of stimulus needed to cause a reaction, i. e. the higher the threshold of stimulation, the lower the excitability; conversely, the lower the threshold of stimulation, the higher the excitability. The threshold of stimulation varies with different stimuli. Receptors are extremely responsive to the effect of adequate stimuli. According to Vavilov, the light-sensitive nerve elements of the retina, the rods, react to eight light quanta, and possibly even to three or four. The energy of the retinal threshold of stimulation is so low that it would take, it has been estimated, 60 million years to raise the temperature of one gramme of water by only one degree Celsius by means of it. The excitability of other receptors is also extremely high: for example, the action of only a few molecules of fragrant substance is enough to stimulate the olfactory cells.

#### EXCITATION

Excited cells have a specific type of response to the effect of stimuli, namely, a wave-like physiological process, *excitation*, that arises in them.

Excitation is a complex biological reaction manifested as a combination of physical, physico-chemical, and chemical processes and functional changes; its imperative sign is a change in the electrical state of the cell-membrane. When stimulated, a cell changes from a state of rest to one of the physiological activity characteristic of it: e. g. a muscle fibre contracts, while a gland cell secretes. Only in nerve cells and nerve fibres is excitation encountered in its pure form, so to say, uncomplicated by other signs of their active state.

A constant difference in electrical potential between the cell cytoplasm and its external environment, i. e. on both sides of the *cell-membrane*, is maintained in a stimulated cell. Thus the cell-membrane is polarized, its internal surface being negatively charged in respect to the outer one. This difference in potential, known as the *membrane potential*, is about seventy or ninety millivolts. It is due to the ion concentration in the cell cytoplasm being different from that outside the cell in the surrounding tissue fluid; the cytoplasm contains more potassium ions and fewer sodium ions than the tissue fluid. In a state of rest the cell-membrane is poorly permeable to sodium ions. With excitation its permeability increases and positively charged sodium ions pass through it into the cell, which leads to a fall in the membrane potential (membrane depolarization), and even to the appearance of a difference in potential of opposite sign.

Changes in the membrane potential during stimulation are known as *action potential*, while the electric current flowing when an excited area of tissue is connected with a non-stimulated one is called the *action current*.

Excitation can be regarded as an explosive process resulting from the change in membrane permeability caused by the effect of a stimulus. The change is relatively small at the beginning and is attended only by slight depolarization and reduction of the membrane potential at the site where the stimulus is applied, and does not spread along the excitable tissue (so-called *local excitation*). Having reached the *critical* or *threshold level*, the changes in potential increase rapidly like an avalanche and become maximal in a short time (in ten milliseconds in a nerve).

Restoration of the initial potential difference, *repolarization* of the membrane occurs at the beginning owing to potassium ions leaving the cell. Later the difference between the ion concentration in the cytoplasm and in the medium surrounding the cell (potassium ions re-enter the cell, while sodium ions leave it) is restored by a special physiological mechanism known as the sodium-potassium pump. The restorative process requires a certain amount of energy which is supplied by metabolic processes.

A feature characteristic of cells when stimulated, i.e. during the period of maximal depolarization of the membrane, is their incap-

city to respond to a new stimulus. The state of non-irritability of a cell during excitation is known as *refractory*.

Excitation is a process that spreads in waves. When it occurs in a cell, or in any part of a cell, e. g. in part of a nerve fibre, it spreads to other cells or to other parts of the same cell. Its spread is due to the action potential that develops in the first cell or part of a cell, becoming in turn a stimulus exciting adjoining areas.

The spread of excitation in nerve fibres and muscles by electricity is distinguished from the transfer of excitation in nerve endings. There the excitation is passed from one nerve cell to another, or from a nerve fibre to a muscle or gland cell, by chemical means. Chemical transmitters of nerve impulses (acetylcholine, noradrenaline) are formed in the nerve ending and cause excitation of the cell on whose surface the ending lies. These transmitters are called *chemical mediators*.

The occurrence and further development of a process of excitation in cells, tissues, or organs is best detected by the registration and measurement of the action potentials. For that reason, electrophysiological methods are widely used both in laboratory experiments and in the clinic.

The electrical manifestations of excitation are now studied by introducing an extremely fine micro-electrode (with diameter of fractions of a micron) into the cell, and placing a second electrode in the surrounding medium. Action potentials can also be registered at the surface of tissues and organs by means of electrodes of much larger diameter. To study the whole organism potentials are registered at the body surface. The electrocardiogram, tracings of the electrical oscillations produced by the work of the heart, is made in this way.

The living cell always responds to a stimulus, whether in the form of excitation accompanied with an electrical reaction, or in the form of constriction or secretion, after a certain *latent period*. This is the interval between the moment the stimulus is applied and the moment the tissue responds to it. The changes required to manifest the reaction take place during it. The latent period of electrical reaction is shorter than that of muscular contraction or secretion. The longest is the secretion reaction.

#### REFLEX REACTIONS

Animals with nervous systems have developed a special type of reaction, *reflexes*, which are responses of the organism involving the nervous system and developing in response to stimulation of the nerve endings or *receptors*.

The nervous system consists of numerous neurones. A *neurone* is a nerve cell with all its processes. Neurones differ in their functional significance, and are divided, in a very rough classification,

into three main groups: 1) *recipient* or *receptor* neurones, 2) *executive* or *effector* neurones, and 3) *contact* neurones.

Receptor neurones have the function of receiving and conveying information on the external world or on the internal state of the organism to the central nervous system. They are located outside the central nervous system in groups of nerves or ganglia. Their processes transmit stimulation from the sensory nerve endings or from cells to the central nervous system. The processes of nerve cells which conduct stimulation from the periphery to the central nervous system are known as *afferent* or *centripetal* fibres.

In response to a stimulus, nerve impulses are discharged rhythmically in the receptors. The information so transmitted is coded in the frequency and rhythm of the impulses.

The various receptors differ in structure and function. Some are located in organs specially adapted to perceiving definite types of stimuli, for example the eye, the optical system that focuses light rays on the retina which harbours sight receptors, or the ear which conducts sound oscillations to sound receptors. Various receptors are adapted to perceive different stimuli adequate to them. They are as follows. 1) *Mechanoreceptors* which react to: a) touch (*tactile receptors*), b) stretch and pressure (*presso-* and *baroreceptors*), c) sound oscillations (*phonoreceptors*) and d) acceleration (*accelero-* or *vestibuloreceptors*); 2) *chemoreceptors* reacting to the stimulation produced by certain chemical compounds; 3) *thermoreceptors* which are stimulated by changes in temperature; 4) *photoreceptors* which perceive light stimuli; and 5) *osmoreceptors* which are stimulated by changes in osmotic pressure.

Some receptors (light, sound, olfactory, gustatory, tactile, temperature), which perceive stimuli from the environment, are located near the surface of the body; they are known as *exteroceptors*. Others receive stimuli associated with changes in the condition and functioning of the organs and of the body's internal environment. They are called *interoceptors* and also include those located in the skeletal muscles and known as *proprioceptors*.

*Efferent neurones* convey impulses along processes (*efferent* or *centrifugal fibres*) passing to the periphery, which cause changes in the condition and function of the various organs. Some are located in the central nervous system, in the cerebrum and spinal cord, each with only one process to the periphery. Such are the motor neurones that cause contraction of the skeletal musculature. Others lie only on the periphery and receive impulses from the central nervous system and convey them to the organs. These form the ganglia of the vegetative nervous system.

The *contact neurones*, which are located in the central nervous system, provide connections between different neurones, serving as a sort of relay station that switches impulses from one neurone to another.

The connections between neurones provide the basis for producing reflex reactions. In each reflex, nerve impulses arising in the receptor upon stimulation are transmitted to the central nervous system along the nerve conductors. There they are switched from the receptor neurone to an effector either directly or by way of the contact neurones and pass to cells on the periphery. Under the effect of these impulses a change takes place in cell activity.

Impulses that reach the central nervous system from the periphery, or are conveyed from one neurone to another, may cause not only stimulation, but also a contrary process, *inhibition*, which is characterized by an arrest or diminution of nervous activity. Inhibition suppresses stimulation and hinders its occurrence. It can also occur in the peripheral organs from the effect of nerve impulses, where it is manifested in a cessation or diminution of function, i. e. of muscular contraction, glandular secretion, etc.

Electrophysiological research has shown that inhibition can be caused by two types of mechanism. With an increase in cell-membrane potential, i. e. with *hyperpolarization* of the cell-membrane, a stronger stimulus is needed to produce excitation, and the nerve impulses may be not strong enough. The second mechanism consists in very frequent nerve impulses reaching the nerve cell from one or more neurones connected with it, and producing a stable depolarization of the cell membrane, i. e. the cell loses its electrical charge and cannot be stimulated. This mechanism was discovered by Vvedensky at the beginning of the century.

Inhibition may also be due to certain chemicals that cause a change in the electrical charge of the cell. They include gamma-aminobutyric acid and several other substances.

The areas of the central nervous system where neurones associated with a reflex lie, in other words, the areas of the cerebrum and spinal cord that receive impulses from definite peripheral receptors and convey them to peripheral organs, are known as *nerve centres*. They are formed by a great number of neurones, which may be located in different parts of the central nervous system. The more complex the reflex, the larger is the number of cells involved in it.

The nerve centres and the executive mechanisms that receive and obey their "commands", the body organs, communicate in a two-way manner during a reflex. The peripheral organs not only receive efferent impulses from the central nervous system but they send afferent impulses back to the centre, signalling the state of their activity. Thus, there is a system of "*feedback*" between the peripheral executive mechanisms and the central nervous system. This type of communication is of particular importance for the performance of movements and is responsible for their exactness and smoothness and for their adjustment to the situation of the moment provoking the movement.

The afferent impulses reaching the central nervous system have a double significance. First, if their frequency is sufficient they are capable of causing urgent activity in a reflex of some sort; second, with a lower frequency, they maintain a relatively constant level of excitation of the nerve centres, alerting them for action. The efferent impulses reaching many body organs from the central nervous system have the same double importance. They may cause a sharp change in activity through the appropriate reflexes, or they keep certain organs and tissues in a state of continuous activity, e.g. continuous tension of the muscles. This continuous level of excitation of the nerve centres or of the activity of organs is known as *tonus*. It may also be maintained by means of certain chemicals that enter the blood stream and act upon the nerve centres and peripheral organs.

The tonus of the nerve centres and of some peripheral organs is a manifestation of homeostasis and one of its causes. Thus, for example, continuous tension of the smooth muscles of the arterial walls conditions the constant level of arterial blood pressure.

Since Pavlov's classic studies, the enormous variety of reflex reactions is divided into two major groups: conditioned reflexes and unconditioned.

*Unconditioned reflexes* are body reactions encountered in all individuals of a species; they are genetically fixed and inborn. Most of them persist in vertebrates after the removal of the cerebral cortex, which shows that they are produced by the action of lower parts of the central nervous system, i. e. by the spinal cord, medulla oblongata, mesencephalon, diencephalon, and the subcortical nuclei of the cerebral hemispheres.

*Conditioned reflexes* are individually acquired reactions, developing in a particular individual during his life, as a result of his experience, and may not be encountered in other individuals of that species. In higher vertebrates conditioned reflexes always occur with the participation of neurones located in the cerebral cortex. They form the basis of higher nervous activity. When they are formed temporary connections arise between the neurones of the cortex. For them to develop, stimulation of a receptor must be associated repeatedly with some form of body activity, with an unconditioned reflex. Then stimulation of the receptor which previously did not cause it begins to produce this form of activity. The activity of any organ of the body can be produced or changed by means of conditioned reflexes, and it is through them that the body functions of higher animals are governed by the cortex, i. e. that the functions are regulated by the cerebral cortex.

Unconditioned and conditioned reflexes underlie the most complex forms of activity of the body as a whole, and of its behaviour in its environment. Conditioned reflexes are the highest form of adaptation of an organism to the external environment.

## CONTROL OF FUNCTIONS

As has already been stated, the characteristic feature of every living organism is that it is a self-regulating system which reacts as a whole to various influences. This is achieved through the interaction of all its cells, tissues, organs, and systems and through the interconnection and intersubordination of all the processes occurring in them. No cell in the organism changes without some other cell also changing. Changes in the functioning of any organ lead to changes in the activity of other organs of one degree or another. This interaction of organs is particularly expressed within a functional system formed of organs whose combined activity is responsible for adaptation to definite environmental conditions.

The interconnection of the functions and reactions of an organism, of its unity and integrity, is due to the presence of two types of mechanisms controlling and correlating them. One of these, the *humoral or chemical mechanism of regulation*, is the more ancient phylogenetically. It is based on the fact that chemical compounds, differing in chemical nature and physiological activity (the products of breakdown and synthesis), form in the various cells and organs during metabolism. Some possess high physiological activity, i. e. very small concentrations of them can effect marked changes in the functions of the organism. Having first entered the tissue fluid and then the blood, they are carried through the entire body by the blood stream and can influence cells and tissues lying some way from those where they were formed. The effect of the chemical stimuli circulating with the blood can be exerted on all cells; to be more precise, chemical stimuli have no definite address. Their effect, nonetheless, differs with the various cells: some cells are more sensitive to one group of chemical stimuli, others to another; and there is a selective sensitivity in cells to them. Being involved in the different links of the chain of metabolism, the various chemical stimuli also differ in their action.

A particular type of chemical control of functions is *hormonal control* effected by the endocrine glands.

The second type of control of functions is the *neural mechanism*, which is much younger physiologically, since it develops later in the course of evolution. It unites, correlates, and regulates the activity of the various cells, tissues, and organs adapting them to the organism's conditions of life. Changes in the activity and state of one group of cells and organs cause reflex changes in the functioning of other cells and organs by way of the nervous system. This mechanism of control is more perfected because, firstly, the cell interaction occurs much more quickly through the nervous system than by means of humoral-chemical mechanisms and, second, the nerve impulses always "remember" a definite "address" (being directed toward definite cells or groups of cells along the neurone processes).

Neural regulation is manifested in changes in cell activity, in the maintenance of a constant level of activity, and in a change in the intensity of the metabolism of rest. The influence of the nervous system on metabolism is regarded as a manifestation of its special *trophic function*.

These two control mechanisms are interconnected. Various chemicals formed in the body influence the nerve cells, causing changes in their state, for example, hormones produced by the endocrine glands affect the nervous system. The humoral mechanism, on the other hand, is to some extent governed by the neural. Thus, the formation and secretion of most hormones occurs under the controlling influence of the nervous system. Consequently, the nervous system influences the functioning of a number of organs not only directly by means of nerve impulses, but also indirectly by means of humoral-chemical stimuli formed in the body cells and secreted into the blood under the effect of nerve impulses.

The activity of the nervous system and the chemical interaction of cells and organs provide one of the most important features of an organism, the *self-regulation of physiological functions*, through which the conditions necessary for the life of the organism are automatically maintained. Any shift in its internal or external environment stimulates activity that results in restoration of stability of the conditions of existence, i. e. in restoration of homeostasis. The higher the development of the organism, the better developed is the self-regulation of functions in it, and the more perfected and stable the homeostasis.

Self-regulation is possible only because reciprocal connections exist between the regulated process and the regulating system. We shall mention only two examples from the many that illustrate this reciprocity. The first is the nerve centres located in the diencephalon which control sodium metabolism by changing the secretion of the adrenocortical hormones (mineralo-corticoids), and thus maintain a constant concentration of sodium in the blood. That is possible only because a shift in sodium concentration causes a change in the condition of the nerve centres which in turn increase or diminish the secretion of adrenocortical hormones. The second example is the muscular movements performed under the effect of impulses reaching the muscles from the central nervous system. Any muscular contraction, in turn, gives rise to a flow of impulses back to the nerve centres, informing the latter of the intensity of the contraction and changing their activity.

In this way there is a cyclic interaction between the regulators and the regulated processes.

## Chapter 3

### BLOOD

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Blood, lymph, and tissue fluid form the *internal environment of the organism*, washing all its cells and tissues. The internal environment is marked by a relative constancy in its composition and physico-chemical properties thanks to which the cells of the organism have relatively constant conditions (homeostasis). This is achieved through the activity of a number of organs which supply the organism with various substances of vital significance and eliminate products of decomposition. In this way, blood plays an essential role in *maintaining homeostasis*, and in preserving a relatively constant water and electrolyte content, in the cells and tissues in particular.

The blood, circulating in the blood vessels, performs a *transport function*. It conveys nutrients to the tissues (glucose, amino acids, polypeptides, fats, vitamins, mineral substances, and water), and the oxygen that enters it in the lungs, and removes "slag", the final products of metabolism (ammonia, urea, uric acid, etc.) and carbon dioxide, which are then eliminated from the body by the kidneys, sweat glands, lungs, and intestines. By this function, the blood plays an important role in humoral regulation, i. e. in the organism's processes of chemical interaction, as it carries hormones and other physiologically active substances from the cells where they are formed to other ones.

Blood performs a *defence function*, being a most important factor of immunity, i. e. of insusceptibility to infection. This is accomplished by the leucocytes in the blood, which are capable of phagocytosis

(p. 80), and by immune bodies that render micro-organisms and their toxins harmless and destroy foreign proteins.

## COMPOSITION, QUANTITY, AND CHEMICAL PROPERTIES OF BLOOD

### COMPOSITION OF BLOOD

Blood consists of a fluid part or plasma, and of formed elements suspended in the latter. These elements are erythrocytes (red blood corpuscles), leucocytes (white blood corpuscles), and platelets.

If blood to which an anticoagulant has been added is poured into a test tube and centrifuged, the formed elements, being heavier, settle to the bottom, and the blood becomes divided into two layers: namely, a red lower layer consisting of the elements, and a transparent, colourless, or slightly yellowish, upper layer consisting of plasma. The leucocytes form a thin white film between the erythrocytes and the plasma since their specific gravity is less than that of the erythrocytes.

By centrifugation in a *haematocrit*, a special graduated capillary tube, it may be seen that plasma constitutes 55 to 60 per cent of the volume of blood, while the formed elements make up the remaining 40 to 45 per cent.

### THE AMOUNT OF BLOOD IN THE BODY

The total amount of blood in the human organism is 6 to 7.5 per cent (about one-thirteenth) of the body weight.

The amount of blood in the human body is determined by means of a harmless colloid dye, e. g. Congo red, which, after being introduced into the blood vessels, leaves the blood stream slowly. A blood sample is taken a few minutes after the dye has pervaded the whole blood system, and the concentration of dye is determined by the colour of the plasma (by comparing its colour with that of a standard solution of the dye). The quantity of blood is determined by a simple calculation. More recently the method of radioactive tracers has been used for this purpose. Blood is taken from the individual being examined, and the erythrocytes separated from the plasma and put into a solution containing radioactive phosphorus. The phosphorus is assimilated by the erythrocytes, which are then re-introduced into the blood stream of the examined individual; after they have spread uniformly the radioactivity of a blood sample is determined, from which the total amount of blood is calculated.

When using these methods, it must be remembered that part of the blood is stored in the "blood depots" (see p. 156) and not included in the circulation. There may therefore be grounds for

thinking that the indicator (dye or labelled erythrocytes) introduced into the blood stream is not distributed quite uniformly throughout the blood. Comparison of the results obtained from these methods in experiments on animals with the results yielded by exsanguination, however, have shown them to be almost identical. The indicators introduced into the blood evidently combine quite rapidly with the blood contained in the depots.

The total volume of blood in the body is maintained at a relatively constant level. With an increase in the fluid part owing to the introduction of substitutes into the blood vessels, the amount of blood rapidly returns to the initial level. Some of the fluid introduced is excreted at once by the kidneys, but the greater part first passes into the tissues, then gradually enters the blood, and is finally excreted by the kidneys. A marked decrease in the amount of blood, owing to profuse haemorrhage, for example, a blood loss amounting to one-third of the total volume, can result in death, and calls for emergency transfusion of blood or blood substitutes.

#### VISCOSITY AND SPECIFIC GRAVITY OF BLOOD

Taking the viscosity of water as unity, the viscosity of blood plasma is 1.7 to 2.2, and the viscosity of whole blood is 5.0. Blood viscosity is conditioned by the presence of proteins and erythrocytes. It increases with an increase in concentration, i. e. with loss of water, for example, during diarrhoea or abundant perspiration, and also with an increase in the number of erythrocytes.

The specific gravity of whole blood is 1.050 to 1.060, of erythrocytes 1.090, and of plasma 1.025 to 1.034.

#### OSMOTIC PRESSURE OF BLOOD

If two solutions of different concentrations, with one containing a larger amount of dissolved substances than the other, are divided by a semi-permeable membrane that permits the passage of the solvent, e. g. water, and not of the dissolved substance, water will pass into the more concentrated solution. The force causing the diffusion of the solvent is known as *osmotic pressure*.

The osmotic pressure of a solution can be measured by means of an osmometer which consists of two vessels separated by a semi-permeable membrane. A highly concentrated solution of a substance is poured into one of the vessels, and a less concentrated solution or the pure solvent into the other. The first vessel is stoppered with a cork into which a vertical manometric tube is inserted. Solvent passes into the vessel containing the solution of higher concentration and the fluid level in the manometric tube rises. The pressure of the water column indicates the value of the osmotic pressure.

The osmotic pressure of blood, lymph, and tissue fluid is important for the regulation of water exchange between the blood and tissues. Changes in the osmotic pressure of the fluid surrounding cells disturb their water exchange. This can be seen from erythrocytes; on being immersed in a solution of NaCl of higher concentration than blood plasma, they lose water, diminish greatly in volume, and shrink. Conversely, erythrocytes placed in a salt solution of a lower osmotic pressure swell, increase in volume, and may finally be disrupted.

The osmotic pressure of blood can be determined by the *cryoscopic method*, i. e. by measuring its freezing point. The higher the osmotic pressure of a solution, i. e. the higher its total concentration of molecules, ions, and colloidal particles, the lower is its freezing point.

The lowering of the freezing point of a molar aqueous non-electrolyte solution below 0°C ( $\Delta t^\circ$ ), in other words its *depression* is 1.85°C, when its osmotic pressure is 22.4 atmospheres. Knowing the freezing point of the solution under test, the value of its osmotic pressure can be calculated.

The *depression of human blood* is 0.56° to 0.58°, consequently, its osmotic pressure is between 7.6 and 8.1 atmospheres. NaCl is responsible for about 60 per cent of this pressure. The osmotic pressure of the erythrocytes and of other body cells is the same as that of the fluid surrounding them.

The osmotic pressure of blood is maintained in mammals and human beings at a relatively constant level, as may be seen from the following experiment. Seven litres of a 5 per cent sodium bisulphate solution were injected into the vein of a horse, which it was calculated would double the osmotic pressure of its plasma. But within ten minutes, the osmotic pressure of the blood plasma had nearly returned to normal, and within two hours was absolutely normal. This occurred because of an abundant excretion of salts in the urine, loose stools, and saliva. The excretions contained chlorides and carbonates as well as the introduced sulphates; sulphates were encountered in the blood even after the osmotic pressure had returned to normal. This showed that normal osmotic pressure is restored first, and the constancy of the blood ion composition only later. The constancy of osmotic pressure is relative since small fluctuations always occur in the organism owing to the passage of substances with large molecules (amino acids, fats, and carbohydrates) from the blood into the tissues, and to the entrance of low-molecular products of cell metabolism into the blood from the tissues.

The excretory organs, particularly the kidneys and sweat glands, are responsible for regulating osmotic pressure. Because of their activity, the metabolic products that are continuously formed in the organism cause no marked influence on its osmotic pressure. In contrast to the osmotic pressure of the blood, that of urine and sweat may fluctuate within quite wide limits. The depression of

sweat is  $0.18^{\circ}$  to  $0.60^{\circ}$ , while that of urine is  $0.2^{\circ}\text{C}$  to  $2.2^{\circ}$ . Intensive muscular work causes particularly marked shifts in blood osmotic pressure.

#### BLOOD pH AND MAINTENANCE OF CONSTANCY

The reaction of blood, conditioned by its concentration of hydrogen ( $\text{H}^+$ ) and hydroxyl ( $\text{OH}^-$ ) ions, is of extremely great biological importance since metabolism normally occurs only at a definite reaction.

Blood has a slightly alkaline reaction. The pH index of arterial blood is 7.4; that of venous blood is 7.35 owing to the large content of carbon dioxide. The pH within cells is somewhat lower, between 7.0 and 7.2, and depends upon cell metabolism and its acid products.

The blood ion concentration is maintained within the organism at a relatively constant level by the buffer properties of the plasma, and erythrocytes and the activity of the excretory organs.

*Buffer properties* are characteristic of solutions consisting of a weak (poorly dissociated) acid and of its salt formed by a strong base. The addition of a strong acid or alkali to such solutions does not bring about a marked shift to acidity or alkalinity as occurs when the same amount of acid or alkali is added to water. This is explained by the fact that the strong acid displaces the weak one in the latter's combination with the base as a result of which a weak acid and a salt of the strong acid are formed in the solution. Thus the buffer solution prevents a shift in ion concentration. The addition of a strong alkali results in the formation of a salt of the weak acid and water, and the possibility of a shift in ion concentration to alkalinity is reduced.

The buffer properties of blood are due to the presence of the following substances, which form what are called buffer systems: 1) carbonic acid and sodium bicarbonate (*carbonate buffer system*) ; 2) monobasic and dibasic sodium phosphate (*phosphate buffer system*) ; 3) plasma proteins (*plasma protein buffer system*); being ampholytes, proteins are capable of detaching both hydrogen and the hydroxyl ions, depending on the ion concentration in the medium ; 4) haemoglobin and potassium salts of haemoglobin (*haemoglobin buffer system*). The buffer properties of haemoglobin, the blood pigment, arise from the fact that, being a weaker acid than  $\text{H}_2\text{CO}_3$ , it gives up potassium ions to the latter and attaches  $\text{H}^+$  ions to itself, thus becoming a very weakly dissociated acid. Haemoglobin accounts for about 75 per cent of blood buffer activity. The carbonate and phosphate buffer systems are much less important in maintaining a constant pH.

The tissues also have buffer systems, and owing to them tissue pH persists at a relatively stable level. Proteins and phosphates are the main tissue buffers. Because of the buffer systems, the carbon

dioxide, and lactic and phosphoric acids, etc. produced in the cells through metabolism, usually cause no marked changes in the pH of the blood when they enter it from the tissues.

A characteristic property of the blood buffer systems is that they ensure a shift of the reaction to alkalinity much more easily than to acidity. Thus, the amount of sodium hydroxide needed to shift the blood plasma reaction to alkaline is 40 to 70 times that required for pure water. Similarly, 327 times the amount of hydrochloric acid must be added to blood plasma, compared with what is needed for water, to cause a shift to acidity. The alkaline salts of the weak acids contained in the blood are known as its *alkaline reserve*, the value of which is determined according to the number of cubic centimetres of carbon dioxide that will combine with 100 millilitres of blood at a carbon dioxide pressure of 40 mm Hg, i. e. close to the partial pressure of carbon dioxide commonly encountered in alveolar air (see p. 181).

Since a definite and quite constant ratio exists between the acid and alkaline equivalents in the blood, the term *acid-base equilibrium of the blood* is accepted.

Experiments performed on warm-blooded animals, and clinical observations, have established the limits of blood pH changes compatible with life. Values of 7.0 to 7.8 would seem to be the extreme limits. A shift of pH beyond them leads to serious disorders and may cause death. A persistent shift of the normal pH of 0.1 or 0.2 in humans can prove fatal.

Despite the presence of buffer systems and of adequate protection of the body from possible changes in blood pH, an increase in acidity or alkalinity may sometimes be encountered under certain physiological conditions, particularly in pathological ones. A shift of reaction to acidity is known as *acidosis*, and a shift to alkalinity as *alkalosis*.

*Compensated* and *non-compensated acidosis* and *compensated* and *non-compensated alkalosis* are distinguished. An actual shift of reaction in either direction is met in the non-compensated forms, which occur when the control mechanisms of the organism become exhausted, i. e. when the blood buffer properties become inadequate and no longer prevent changes in reaction. Compensated acidosis or alkalosis is more frequent and is not attended by a shift in active reaction, but it is marked by decreased buffer activity of the blood and tissues, which creates a danger of the compensated form becoming non-compensated.

Acidosis may be due, for example, to an increase in the carbon dioxide content of the blood or to a decrease in the alkaline reserve. The first type, *gaseous acidosis*, is encountered in impaired elimination of carbon dioxide through the lungs, in diseases of the lungs, for example. The second type, *non-gaseous acidosis*, develops when an excess amount of acid accumulates in the body, as in diabetes

and diseases of the kidneys. Alkalosis may also be gaseous (intensified elimination of carbon dioxide) or non-gaseous (increased alkaline reserve).

Changes in the blood alkaline reserve, and slight changes in its pH are constantly taking place within the capillaries of the systemic and pulmonary circulations. Thus, large amounts of carbon dioxide enter the blood in the tissue capillaries and acidify the venous blood by a pH of 0.01 to 0.04 compared to the reaction of the arterial blood. Conversely, a shift toward alkalinity occurs in the pulmonary capillaries owing to the passage of carbon dioxide into the alveolar air.

The activity of the respiratory apparatus, which ensures the elimination of excess carbon dioxide by intensifying lung ventilation, is important for the maintenance of a constant blood reaction. The kidneys and the gastro-intestinal tract are also significant in this respect as they eliminate excess acids and alkalis from the body.

With a shift of the reaction toward acidity, the kidneys eliminate an increased amount of monobasic sodium biphosphate in the urine, while with a shift to alkalinity they discharge large amounts of alkaline salts (disodium hydrogen phosphate and sodium bicarbonate). In the first case the urine becomes markedly acid, and in the second, alkaline (in normal conditions the pH of the urine is between 4.7 and 6.5, but in disorders of acid-base equilibrium it may vary between 4.5 and 8.5).

A relatively small amount of lactic acid is also eliminated by the sweat glands.

#### COMPOSITION OF BLOOD PLASMA

Blood plasma consists of 90 to 92 per cent water and 8 to 10 per cent dry matter, mainly proteins, and salts. It contains several proteins differing in their properties and functional importance: viz. albumins (about 4.5 per cent), globulins (1.7 to 3.5 per cent), and fibrinogen (about 0.4 per cent).

The total protein content of human plasma averages 7 to 8 per cent; the remaining amount of dry matter is made up of other organic substances and mineral salts.

Plasma contains non-protein nitrogenous compounds, namely, products of hydrolytic breakdown of proteins, which are absorbed in the alimentary tract and utilized by the cells to synthesize the proteins of protoplasm (amino acids and polypeptides), and products of protein decomposition destined to be eliminated from the organism (urea, uric acid, creatine, creatinine, and ammonia).

The total amount of *non-protein nitrogen* in the plasma is 30 to 40 milligrams per 100 millilitres of which half is urea. When the kidneys are not functioning properly the amount of plasma non-protein nitrogen increases markedly.

There are also nitrogen-free organic substances in the plasma namely, glucose (85 to 110 milligrams per 100 millilitres) which is the principal source of energy for cells of the organism, and various organic acids produced as a result of cell activity, for example, lactic acid.

Mineral substances constitute about 0.9 per cent of the blood plasma. They are mainly  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ , and  $\text{Mg}^{++}$  ions and  $\text{Cl}^-$ ,  $\text{HPO}_4^-$ , and  $\text{HCO}_3^-$ .

#### IMPORTANCE OF PLASMA MINERALS AND BLOOD SUBSTITUTES

Artificial solutions with an osmotic pressure, i. e. salt concentration, equal to that of the blood, are known as *isosmotic* or *isotonic*. An 0.9 per cent  $\text{NaCl}$  solution is isotonic for warm-blooded animals and man. Solutions with an osmotic pressure greater than that of the blood are called *hypertonic*, and those with a lesser pressure, *hypotonic*.

An isotonic  $\text{NaCl}$  solution will support the vital activity of separate organs for some time, for example the isolated heart (removed from the body) of a frog. It is not completely physiological, however, and the heart cannot function for a lengthy period with a solution containing only  $\text{NaCl}$  circulating through it. The addition of a small quantity of  $\text{KCl}$  and  $\text{CaCl}_2$  to the solution restores an arrested heart to activity and it can continue to function for some time. Thus, not only is the state of isotonia important, but also the qualitative composition of the solution. In view of that, formulae for solutions have been worked out that are similar to plasma in content of certain salts, and therefore more "physiological" than an isotonic solution of  $\text{NaCl}$ .

Many solutions have been proposed that are used in physiological experiments and in clinical practice (they are introduced into the body subcutaneously or intravenously, for instance, in the presence of various medical indications). *Ringer's*, *Locke's*, and *Tyrode's* solutions are those most widely used.

#### Composition of Various Physiological Solutions

Solution	$\text{NaCl}$	$\text{KCl}$	$\text{CaCl}_2$	$\text{NaHCO}_3$	$\text{MgCl}_2$	$\text{NaH}_2\text{PO}_4$	Glucose
	grammes	per	litre	of	distilled water		
Ringer's solution for cold-blooded animals	6.5	0.14	0.1-0.12	0.2	—	—	—
Locke's solution for warm-blooded animals	9.0	0.42	0.24	0.15	—	—	1.0
Tyrode's solution	8.0	0.2	0.2	0.1	0.1	0.05	1.0

Physiological solutions employed to maintain the activity of isolated organs of warm-blooded animals are saturated with oxygen.

Physiological solutions are not of equal value to blood plasma, however, because they do not contain such colloidal substances as plasma proteins. Therefore various colloids, e.g. water-soluble high-molecular polysaccharides (with a molecular weight of 13,000 to 100,000 and higher) or specially treated protein preparations are added to a saline glucose solution (one such preparation with polysaccharides is called *dextran*). The colloids are added to an amount of 7 to 8 per cent. These solutions are introduced into patients to restore blood pressure after loss of blood. Although these solutions are available, however, the best substitute for blood is plasma.

Animal blood plasma cannot be introduced into the blood of humans because of species differences in the blood and tissue proteins. Various pathological reactions (anaphylactic shock and serum sickness, see p. 82) can be caused in an animal organism by the introduction of proteins derived from an animal of another species. Methods of treating animal plasma have been elaborated that deprive the proteins of their specific species distinctions, and plasma so treated can be introduced into the blood of a human being.

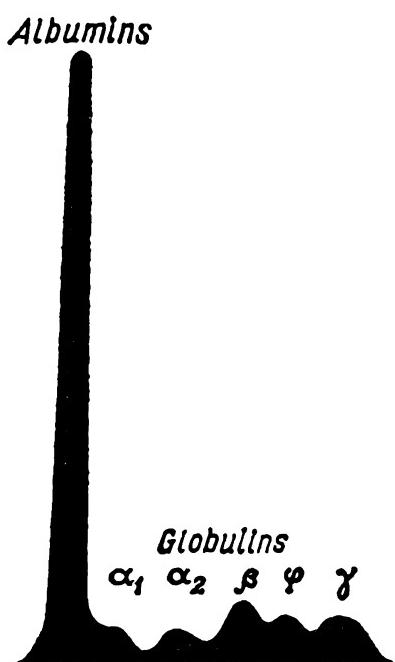
#### PROTEINS OF BLOOD PLASMA

The significance of plasma proteins is multiform. 1. They are responsible for oncotic pressure (see the next section), the level of which is important for regulating water exchange between blood and tissues. 2. Because they possess buffer properties, they maintain the acid-base equilibrium of blood. 3. They produce a definite viscosity of the plasma, which is important in maintaining blood pressure (see p. 56). 4. Proteins promote stabilization of the blood by providing conditions that prevent sedimentation of erythrocytes. 5. Proteins play an important role in coagulation. 6. Plasma proteins are important factors in immunity.

There is a score or more of various proteins in blood plasma. They fall into three main groups: albumins, globulins, and fibrinogen. Since 1937 plasma proteins have been separated by electrophoresis, a method based on the fact that various proteins display different mobility in an electric field. Globulins by this means are separated into several fractions: alpha<sub>1</sub>-( $\alpha_1$ -), alpha<sub>2</sub>-( $\alpha_2$ -), beta-( $\beta$ -), and gamma-( $\gamma$ -) globulins. The electrophoretic diagram of plasma proteins is shown in Fig. 1.

Gamma globulins have great importance in protecting the organism against viruses and bacteria, and their toxins. This is because the so-called antibodies being mainly  $\gamma$ -globulins. On being introduced into patients, they raise body resistance to infection. *Properdin*, a

FIG. 1. Electrophoretic pattern of human blood plasma proteins



protein complex that has a similar effect, has also been found in the plasma.

The ratio between the different protein fractions changes in certain diseases, and for that reason their measurement has diagnostic value.

The main site of formation of these proteins is the liver, where the albumins and fibrinogen are synthesized. Globulins are synthesized not only in the liver, but also in the bone marrow, spleen, and lymph nodes, i. e. in organs belonging to the reticulo-endothelial system. There are between 200 and 300 grammes of proteins in the total volume of blood plasma. Owing to their continuous synthesis and decomposition protein metabolism proceeds rapidly.

#### OSMOTIC PRESSURE OF PLASMA PROTEINS

Osmotic pressure is created not only by the crystalloids dissolved in blood plasma, but also by colloids, the plasma proteins. The pressure produced by the latter is known as *oncotic pressure*.

Although the absolute quantity of the proteins in plasma is 7 to 8 per cent, which is nearly ten times the amount of dissolved salts, the oncotic pressure due to them is only about 0.5 per cent of the osmotic pressure of the plasma (equal to 7.6 to 8.1 atmospheres), i. e. 0.03 to 0.04 atmospheres (25 to 30 mm of mercury). This is because the protein molecules are very large and they are much less in number than the crystalloid molecules.

Despite its negligible value, however, oncotic pressure is exceptionally important for exchange of water between the blood and the tissues. It influences those physiological processes that are based on filtration phenomena (the formation of interstitial fluid, lymph, and urine, and the absorption of water in the intestines). The large

molecules of the plasma proteins do not penetrate the endothelial wall of capillaries, as a rule, and remain in the blood stream, retaining a certain amount of water in the blood (corresponding to the magnitude of their osmotic pressure). In this way they help maintain the relative constancy of the water content of blood and tissues. Their ability to retain water in the blood stream can be demonstrated by the following experiment. If a dog is bled repeatedly and its erythrocytes (separated from the plasma in a centrifuge) re-introduced into the blood stream with a saline solution, the level of blood proteins is greatly reduced, and causes marked swelling (oedema) in the animal. Experiments have shown that prolonged perfusion of isolated organs with either Ringer's solution or Locke's leads to the development of tissue oedema, which may be arrested, however, by substituting blood serum for the physiological solution. That explains the need to introduce colloidal substances into blood substitutes, matching their oncotic pressure and viscosity so that they are identical to those of blood.

#### COAGULATION OF BLOOD

The coagulation of blood, or its transformation from a fluid into a jelly-like clot, is a biologically important defence reaction of the organism against loss of blood.

A blood clot, or *thrombus*, forms at the site of an injury to a small blood vessel, and acts as a plug sealing the vessel and stopping further bleeding. A decrease in the capacity of the blood to coagulate, however slight the injury, can cause a fatal haemorrhage.

Human blood escaping from the blood vessels begins to coagulate in three or four minutes and solidifies completely into a gelatinous mass within five or six minutes. With an injury to the inner coat (*tunica intima*) of the blood vessel, or with an increase in its coagulable properties blood may coagulate within the blood vessels of an intact organism, in which case the thrombus forms within the vessels.

Changes in the physico-chemical state of *fibrinogen*, one of the proteins in the plasma, are responsible for coagulation. The fibrinogen changes from its soluble form to an insoluble one, turns into *fibrin*, and forms a clot.

Fibrin precipitates as long thin threads, that form nets in the loops of which formed elements get caught. If blood discharged from a blood vessel is whipped, most of the fibrin formed will be left on the whisk. Washed free of erythrocytes fibrin is white and of a fibrous structure.

Blood so deprived of fibrin is called *defibrinated*, and consists of formed elements and blood serum. Thus *blood serum* differs in composition from plasma in the absence of fibrinogen.

Serum can be separated from a clot if a test tube of coagulated blood is allowed to stand for some time. The clot becomes dense and shrinks, and a certain amount of serum is squeezed from it.

Plasma, as well as whole blood, is capable of coagulation. Plasma, that is separated from the formed elements by centrifugation in cold (a method that prevents coagulation) and then heated to 20° or 35°C, coagulates rapidly.

Several theories have been advanced to explain the mechanism of coagulation. That most commonly accepted is the enzyme theory the basis of which was laid by Schmidt about a century ago.

According to this theory, the final stage in coagulation is the conversion of the fibrinogen dissolved in the plasma into insoluble fibrin by an enzyme *thrombin* (Fig. 2, stage III).

There is no thrombin in circulating blood. It is formed from *prothrombin*, a plasma protein synthesized in the liver. To form thrombin an interaction is required between prothrombin and *thromboplastin* in the presence of calcium ions (Fig. 2, stage II).

Circulating blood also contains no thromboplastin, which is only formed after the destruction of blood platelets (*blood thromboplastin*) or through injury to tissues (*tissue thromboplastin*).

The formation of the intrinsic thromboplastin begins with the destruction of blood platelets, and the interaction of substances produced by that process with the globulins in the plasma, i. e. with factor V (otherwise known as *globulin accelerator*), *antihaemophilic globulin* (also called *thromboplastinogen*), and also with another substance contained in the plasma, called the *plasma thromboplastin component* (also known as the *Christmas factor*). The presence of calcium ions is also essential to form intrinsic thromboplastin (see Fig. 2, stage I, on the left).

The tissue thromboplastin is formed through the interaction of substances produced by damaged tissue cells with the factor V mentioned above and with another blood plasma globulin, *factor VII*, or *proconvertin*, and also in the presence of calcium ions (Fig. 2, stage I, on the right).

With the formation of thromboplastin, the process of coagulation rapidly begins.

The scheme presented here is far from complete, since a much greater number of different substances actually take part in the process.

If blood does not contain the antihaemophilic globulin involved in thromboplastin formation, *haemophilia* occurs, a disease characterized by greatly reduced capacity of the blood to coagulate. With it even a small injury can lead to a dangerous loss of blood.

Chemical methods have been elaborated to extract thrombin from plasma and to produce it in large quantities (Kudryashov). The preparation accelerates coagulation significantly. Thus, its

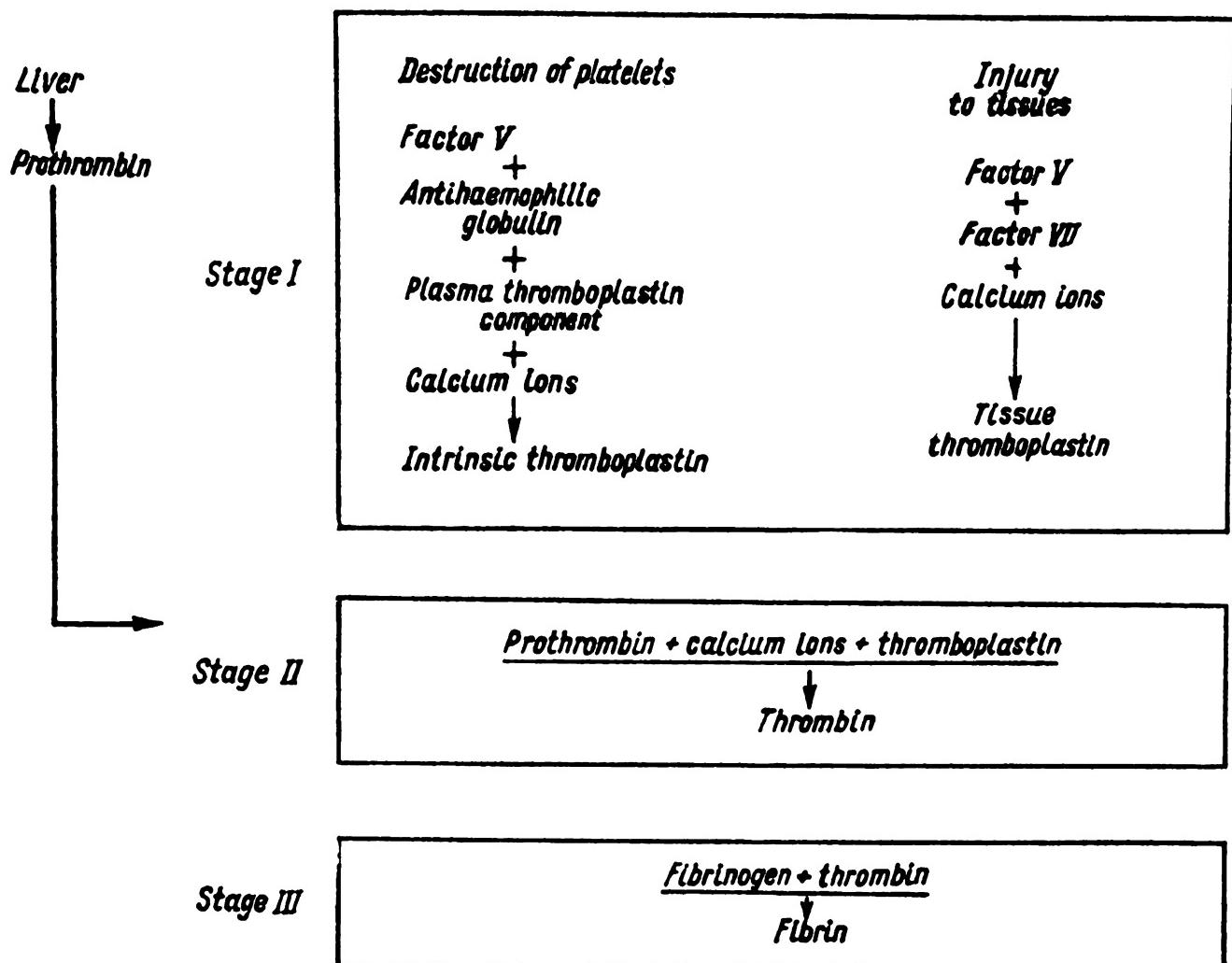


FIG. 2. Schematic representation of coagulation of the blood

addition to oxalated blood in which no thrombin has formed because the calcium has been precipitated, causes coagulation in the test tube within two or three seconds. If haemorrhage from an injured organ (e. g. the liver, spleen, or brain) cannot be stopped by tying the blood vessels, it can be arrested rapidly by applying gauze soaked in thrombin solution to their surface.

After fibrinogen has been converted to fibrin, the clot formed becomes dense, and shrinks, or undergoes *retraction*, a process due to a substance known as *retractozyme* which is released during the disintegration of blood platelets. It has been demonstrated in experiments on rabbits that, although with a sharp decrease in the number of platelets blood may coagulate, the clot does not thicken, but remains loose and does not ensure adequate closure of the injured blood vessel.

Coagulation is altered by the influence of the nervous system. It is accelerated by pain stimuli, which prevents loss of blood. Stimulation of the superior cervical ganglion reduces coagulation time but its removal extends it.

Coagulation can also be altered by a conditional reflex. For instance, if a signal that exerts no direct influence on coagulation is

combined repeatedly with a pain stimulus, it will cause acceleration of coagulation when applied alone. One can assume, that some sort of substances that accelerate coagulation are formed in the organism through stimulation of the nervous system. It is known, for example, that adrenaline (epinephrine), secretion of which by the adrenals is stimulated by the nervous system and increases under the effect of pain stimuli and emotion, accelerates coagulation of the blood. At the same time, it causes constriction of the arteries and arterioles, and so contributes to lessening of the haemorrhage from injured vessels. The adaptational significance of these phenomena is evident.

A number of physical factors and chemical compounds hamper coagulation; the effect of cold, which markedly delays the process, should be noted above all.

Coagulation is also delayed if blood is poured into a glass vessel with walls covered with paraffin or silicone to prevent them being wetted by the blood. In such a vessel blood may remain fluid for several hours. The disintegration of blood platelets and consequent liberation into the blood of the substances which participate in thrombin formation is greatly hampered in these conditions.

Oxalic and citric acids prevent coagulation. Sodium citrate added to blood binds calcium ions, while ammonium oxalate causes precipitation of calcium, so that formation of thromboplastin and thrombin becomes impossible. Oxalates and citrates are used to prevent coagulation of the blood only outside the organism; they cannot be introduced into it in any amount because the resultant binding of blood calcium leads to severe disorders in vital activity.

Certain substances known as *anticoagulants* completely prevent coagulation. They include *heparin* which occurs in the tissues of the liver and lungs and *hirudin* which is secreted by the buccal glands of leeches. Heparin interferes with the action of thrombin on fibrinogen and suppresses the activity of thromboplastin. Hirudin suppresses the third stage of coagulation by hindering fibrin formation.

There are other anticoagulants that have an indirect effect. While not directly influencing the process of coagulation, they depress the formation of substances that take part in it. They include synthetically derived preparations (dicumarol, pelentan, etc.) which block the synthesis of prothrombin and factor VII in the liver.

The serum proteins include yet another substance, namely *fibrinolysin*, an enzyme that occurs in an inactive form in plasma, and dissolves fibrin being formed. Its precursor, *profibrinolysin*, is activated by the *fibrinokinase* encountered in many body tissues.

Thus it follows that two systems are simultaneously present in blood: *coagulative* and *anticoagulative*. In normal conditions they are balanced in a certain manner, that prevents intravascular coagulation, and this balance is impaired in some diseases, and by injuries.

The significance of the physiological anticoagulative system has been demonstrated by Kudryashov, who showed in experiments that rapid intravenous injection of a sufficient dose of thrombin will cause the death of an animal from intravascular coagulation. When the same lethal dose of thrombin is introduced slowly, however, the animal does not die, but its blood loses its coagulability to a significant degree.

This permits us to conclude that injection of thrombin leads to the appearance in the organism of substances that delay coagulation, the secretion of which is controlled by the nervous system. With a slow intravenous introduction of thrombin into a rat, blood coagulated only within the vessels of a previously denervated limb. It is thought that the increased level of thrombin in the vascular blood stream causes a reflex secretion of coagulation-inhibiting substances by the walls of the vessels. Cutting of the nerves suppresses this reflex as does exposure to the effects of narcotics.

#### FORMED ELEMENTS OF THE BLOOD ERYTHROCYTES

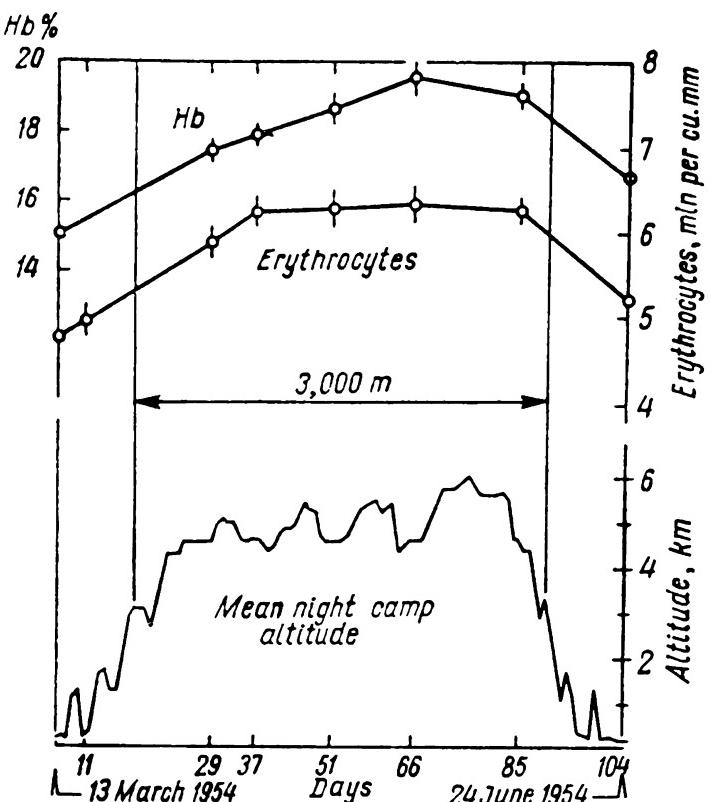
*Erythrocytes* or *red blood corpuscles* are cells in humans and warm-blooded animals that have a homogenous protoplasm but no nucleus.

A *stroma*, the framework of the cell, and a *membrane*, are distinguished in an erythrocyte. The membrane is composed of lipoprotein complexes and is non-permeable for colloids and  $K^+$  and  $Na^+$  ions but easily permeable for  $Cl^-$  and  $HCO_3^-$  anions, and also for  $H^+$  and  $OH^-$ . The mineral composition of erythrocytes and plasma is not identical; human erythrocytes contain more potassium than sodium, while the proportion of these salts in plasma is reversed. Haemoglobin constitutes 90 per cent of the dry matter of erythrocytes, while other proteins, lipoids, glucose, and mineral salts make up the remaining 10 per cent.

Determination of the number of erythrocytes in blood (which is done under a microscope with the aid of counting chambers or automatic electronic instruments) has acquired great importance in both physiology and clinical practice.

There are around five million erythrocytes in a cubic millimetre of the blood of a healthy man, and about 4,500,000 in that of a woman. The number of erythrocytes in the blood of a newborn infant exceeds that in adults.

The quantity of erythrocytes in blood can vary. It increases with low barometric pressure (at great heights) during muscular work or emotion, and when the body loses much water. The increase may persist for varying lengths of time, and may not always indicate an increase in the total number of erythrocytes in the body. Thus,



**FIG. 3.** Alterations in the haemoglobin level and erythrocyte count in members of a high-altitude expedition, depending on the altitude above sea level (after Pace et al.)

with a large water loss due, for example, to excessive perspiration, a short-term thickening of the blood occurs and the number of erythrocytes per unit volume increases although their absolute number in the body does not change. With emotional excitation or strenuous physical work the number of erythrocytes in the blood increases due to contraction of the spleen and the liberation of blood rich in erythrocytes into the systemic blood stream from the blood depot of the spleen (see p. 156).

The increase in the number of erythrocytes in the blood of an individual under low barometric pressure is caused by the diminished oxygen supply in the blood. People living at high altitudes have a higher erythrocyte content due to intensified production of red blood corpuscles in the bone marrow, an organ of blood formation (Fig. 3). Not only is there an increase in the number of erythrocytes per unit volume of blood, but there is also an increase in the total number in the body.

Reduction of the number of erythrocytes, or *anaemia*, is encountered after blood loss, or as a result of their intensified disintegration, or owing to a fall in their production.

The diameter of an erythrocyte is between 7.2 and 7.5 microns, and its volume averages 88 to 90 cubic microns. The size of each erythrocyte and their total number determine the value of their total surface area, which is very important since it is the area involved in the absorption and liberation of oxygen, which is their principal physiological function.

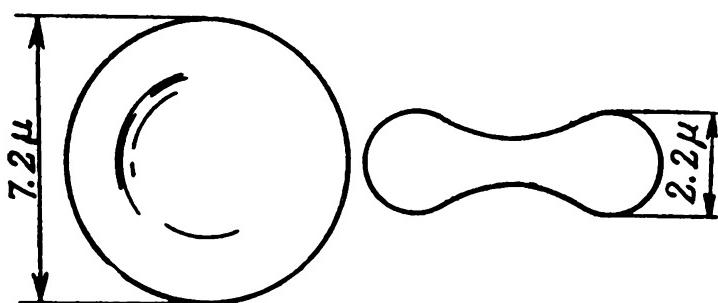


FIG. 4. Diagrammatic representation of an erythrocyte

The sum of the total surface of all erythrocytes in the blood of a human is 3,000 square metres on the average, i. e. 1,500 times the entire surface of the body. The peculiar shape of an erythrocyte contributes to this large surface. Human erythrocytes are flattened and have a concaved centre on both surfaces (Fig. 4). With that shape, no point of the cell is located further than 0.85 micron from its surface; with a spherical shape the centre would be 2.5 microns from the surface and the total area would be 20 per cent less. The actual ratio between surface and volume facilitates better performance of their function of transporting oxygen from the respiratory organs to the body cells.

That function is fulfilled by means of the respiratory pigment of blood, *haemoglobin*, present in erythrocytes. The fact that haemoglobin is contained within the red blood corpuscles and not dissolved in the plasma, is of great physiological significance and is as follows.

1. The viscosity of the blood is thereby reduced. It has been calculated that the same amount of haemoglobin dissolved in the plasma would increase viscosity by several times and severely hamper the work of the heart and circulatory system.

2. The oncotic pressure of plasma is reduced, which is important for the prevention of dehydration of tissues (due to escape of water into the plasma).

3. Optimal conditions are created through a special chemical medium within the erythrocyte, for the binding of oxygen by haemoglobin.

#### HAEMOGLOBIN

Haemoglobin performs the important role in the organism of oxygen-carrier and takes part in the transport of carbon dioxide. It is a complex chemical compound (with a molecular weight of 68,800) consisting of a protein *globin* and four molecules of *haeme*. A haeme molecule contains an atom of iron which is able to combine with, and give up, oxygen. The valency of iron does not change after combining with oxygen, but remains bivalent.

If haemoglobin is treated with a hydrochloric acid solution the haeme is split off from the globin. Combining with the hydrochloric acid, it is converted to haemin ( $C_{34}H_{32}N_4O_4FeCl$ ) which forms

characteristically shaped crystals. This test for haemin is used in forensic medicine to prove the presence of blood.

A haeme molecule is composed of four pyrrole rings (two alkaline and two acid). The atom of iron in haeme binds it to the protein part of the globin. When haeme loses its iron but retains its pyrrole structure *haematoporphyrin* is formed. That occurs in large amounts in the organism during certain forms of poisoning or during metabolic disorders; the haematoporphyrin is eliminated in the urine.

The haeme is the *active*, or *prosthetic group*, of haemoglobin, while globin is a protein haeme-carrier. On combination with oxygen, haemoglobin is converted to *oxyhaemoglobin* (designated by the symbol  $\text{HbO}_2$ ). Oxyhaemoglobin which has given up its oxygen is known as *reduced haemoglobin* (Hb). Oxyhaemoglobin, haemoglobin, and certain other haemoglobin compounds and derivatives have characteristic bands in their absorption spectrum. Thus, when a ray of light is passed through a solution of oxyhaemoglobin, two characteristic dark absorption bands are encountered in the yellow-green part of the spectrum between Fraunhofer's lines D and E. Reduced haemoglobin has a single wide absorption band in the yellow-green part (Fig. 5).

Oxyhaemoglobin differs somewhat in colour from haemoglobin, and because of that arterial blood containing oxyhaemoglobin is bright red, and the greater its saturation with oxygen, the brighter it is. Venous blood which contains a large amount of reduced haemoglobin is dark-cherry in colour.

The more pronounced ability of haemoglobin to absorb light rays with a wave-length of 620 to 680 millimicrons compared with oxyhaemoglobin is the basis of *oxyhaemometry*, a method used to measure the degree of oxygen saturation of blood. The method consists in passing the rays of a small electric lamp through the pinna of the ear, or through a cuvette filled with blood, and determining the intensity of the luminous flux of the given wave length by means of a photocell. The degree of saturation of the blood with oxygen is determined from the photocell readings.

The blood of adults contains 14 to 15 per cent of haemoglobin on average (13.5 to 16 per cent in men and 12.5 to 14.5 per cent in women). The total haemoglobin content is approximately 700 grammes.

During the embryonic period human blood has various types of haemoglobin which are differentiated by their ability to combine with oxygen and by certain other chemical properties. These types are determined and separated by measuring the optical density of haemoglobin solutions before and after denaturation with caustic alkali. The different types of haemoglobin are designated HbA, HbF, HbP. Haemoglobin P (HbP) is encountered only during the first seven or twelve weeks of intra-uterine development of the embryo. Haemoglobin F (HbF), or foetal haemoglobin, and haemo-

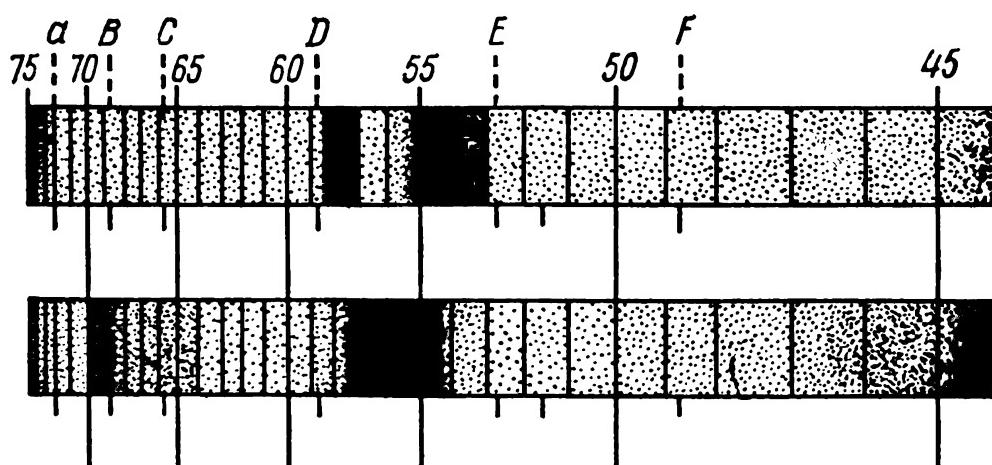


FIG. 5. Absorption spectra of oxyhaemoglobin (top) and haemoglobin

globin A (HbA), or adult haemoglobin, appear in the blood of the foetus in the ninth week. Of essential importance is the fact that foetal haemoglobin has a greater affinity for oxygen and can become saturated to 60 per cent at an oxygen pressure at which the haemoglobin of the mother will saturate only to 30 per cent. The various species of vertebrates differ in haemoglobin structure, the different types of haemoglobin possessing identical haeme but varying in the amino acid composition of their globulins.

Haemoglobin synthesis and decomposition associated with the formation and destruction of erythrocytes occur continuously in the organism. Synthesis takes place in the erythroblasts of the red bone marrow. Haemoglobin is liberated from red blood corpuscles on their destruction in the reticulo-endothelial system, mainly in the liver and the spleen. There the iron splits off from the haeme and, after subsequent oxidation, the pigment bilirubin is formed from haemoglobin and is discharged in the bile into the intestine where it is converted to stercobilin and urobilin and excreted in the faeces and urine. About eight grammes of haemoglobin, i. e. a little more than one per cent, are destroyed and converted to bile pigments every 24 hours.

Other haemoglobin compounds may be formed in human and animal organisms, each with a characteristic absorption spectrum. This group includes methaemoglobin and carboxyhaemoglobin which are formed as a result of certain types of poisoning.

*Methaemoglobin* (MetHb) is a stable combination of haemoglobin with oxygen during the formation of which the valency of the iron changes; the bivalent iron of the haemoglobin molecule is transformed to the trivalent form. With accumulation of large amounts of methaemoglobin in the blood, oxygen cannot be released to the tissues and death results from asphyxia.

Methaemoglobin differs from haemoglobin in its brown colour and in the presence of absorption bands at the red end of the spectrum.

It is formed through exposure to the effect of strong oxidizing agents, such as ferricyanide (red blood salt), potassium permanganate, amyl nitrite, propyl nitrite, aniline, potassium chlorate, and phenacetin (acetophenetidin).

*Carbohaemoglobin* (HbCO) is a compound formed of haemoglobin iron and carbon monoxide (CO). It is about 150 to 300 times as stable as the compound of haemoglobin and oxygen and because of that even a 0.1 per cent admixture of carbon monoxide in the air inhaled leads to a condition in which 80 per cent of the haemoglobin is bound to carbon monoxide and cannot combine with oxygen, which is fatal.

Weak poisoning with coal gas is a reversible process. With inhalation of fresh air, carbon monoxide splits off gradually from the carboxyhaemoglobin and is eliminated.

Breathing of pure oxygen gives a twentyfold increase in the rate of carboxyhaemoglobin splitting. With severe poisoning it is necessary to apply artificial respiration with a gaseous mixture containing 95 per cent oxygen and 5 per cent carbon dioxide, and by blood transfusion.

*Myoglobin* is a muscular haemoglobin that occurs in skeletal muscles and in the myocardium. Its prosthetic group, the haeme, is identical with that of haemoglobin, but its protein part, globin, has a lower molecular weight.

Human myoglobin is capable of binding 14 per cent of all the oxygen in the organism. This property is important for the supply of oxygen to the working muscles. Even when blood flow is arrested in some parts of the muscle through compression of the capillaries during muscle contraction, an oxygen supply is maintained for some time to its fibres by the oxygen combined with myoglobin.

#### HAEMOLYSIS

Haemolysis is the destruction of the erythrocyte membrane and the release of haemoglobin into the blood plasma, which turns red and becomes transparent (laky blood). The stroma of the destroyed and haemoglobin-free erythrocyte forms a so-called blood shadow or phantom corpuscle.

Haemolysis may occur either within body or outside (in a test tube) from a number of causes. If the osmotic pressure inside erythrocytes suspended in a hypotonic solution is greater than that of the surrounding fluid, the water will enter the erythrocytes from the solution as a result, and they swell and their membranes burst. This phenomenon, known as *osmotic haemolysis*, is encountered when the osmotic pressure of the surrounding solution falls to half the normal. When suspended in a slightly hypotonic saline solution, however, erythrocytes are not destroyed but only swell and become somewhat larger.

The NaCl concentration of the solution at which haemolysis begins is the measure of the index of the *osmotic fragility* of erythrocytes. Haemolysis begins in human blood in a 0.4 per cent solution of NaCl, and all its erythrocytes are destroyed in a 0.34 per cent solution. In various pathological conditions the osmotic fragility of the erythrocytes may be increased and complete haemolysis will occur even in solutions with a high NaCl concentration.

Haemolysis can also be caused by the effect of certain chemicals, for example, by solvents of lipoids—ether, chloroform, benzol, and alcohol, which are destructive (in high concentrations) of the erythrocyte membrane, and also by the effect of bile acids, saponin, pyrogallol, and certain other substances.

Destruction of red blood corpuscles can occur outside the organism through the action of strong mechanical factors, when an ampule of blood is shaken. Repeated freezing and thawing of blood also leads to haemolysis.

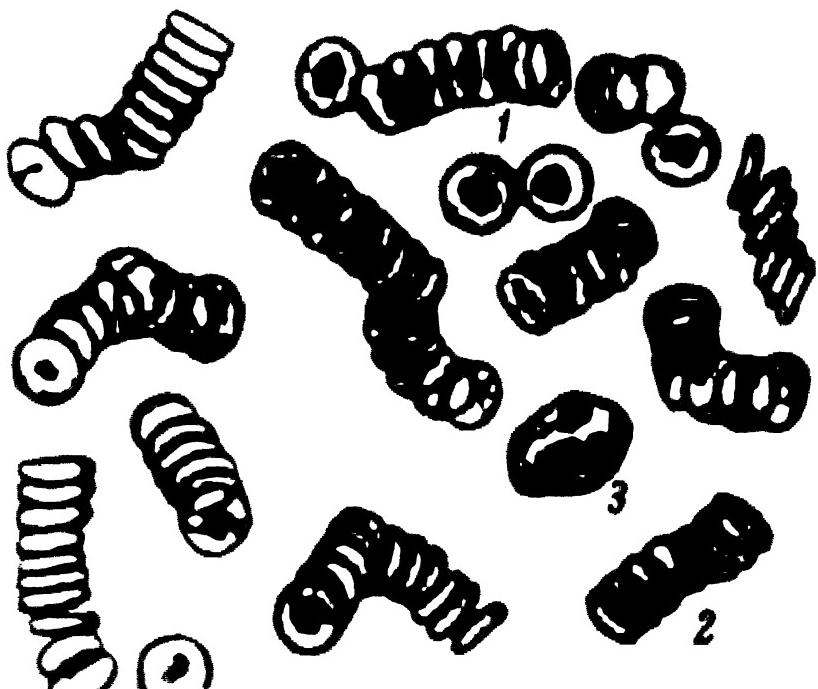
Haemolysis can occur within the organism under the influence of certain types of snake poisons or through the action of *haemolysins*, special substances that form in the plasma as a result of repeated introduction of erythrocytes derived from other animals. Haemolysins have species specificity, and affect the erythrocytes only of the species, whose blood has been introduced into the organism. Thus, the blood serum of a normal rabbit exercises a weak haemolytic action on sheep erythrocytes, but complete haemolysis is caused even by a 90 per cent dilution of serum derived from a rabbit after sheep red blood corpuscles have been repeatedly introduced into its blood.

#### ERYTHROCYTE SEDIMENTATION RATE (ESR)

Blood to which anticoagulants have been added will settle in a test tube after a certain time, and its erythrocytes be deposited as a sediment (erythrocyte sedimentation reaction).

The phenomenon can be studied as follows. Blood is mixed with a sodium citrate solution and then aspirated into a glass capillary tube graduated in millimetres. The height of the upper transparent layer formed within a certain period of time is measured. The normal rate of erythrocyte sedimentation is three to nine millimetres per hour for men, and seven to twelve millimetres for women; during pregnancy it may reach 45 millimetres per hour. With new-born infants the ESR is only 0.5 millimetres per hour. ESR values above nine millimetres per hour in men and 12 millimetres in non-pregnant women are evidence of the presence of disease.

The ESR depends on the properties of plasma. For instance, erythrocytes derived from a man and placed in male blood plasma settle at a rate of five to nine millimetres per hour, but those placed in the plasma of a pregnant woman will settle at a rate up to 50



**FIG. 6. Blood viewed in a microscope**

1 — single erythrocytes;  
2 — erythrocytes arranged in "rouleaux"; 3 — leukocytes

millimetres per hour. Similarly, erythrocytes obtained from a woman settle in male plasma at a rate around nine millimetres per hour, and in the plasma of a pregnant woman, at a rate above 60 millimetres per hour.

If erythrocytes remained separate, i. e. did not adhere to one another, their rate of sedimentation would be 0.2 millimetres per hour. The high rate is caused by their piling up one on top of the other in "rouleaux" resembling piles of coins (see Fig. 6).

With a sedimentation rate of one millimetre an hour the rouleaux consist of about eleven erythrocytes, but at a rate of 75 millimetres per hour the clumps have a diameter of 100 microns or more, and are formed by an immense number of red blood corpuscles (up to 60,000). An increase in the globulin content of the blood plasma is presumed to be the cause of the accelerated rate of sedimentation.

#### BLOOD GROUPS

In 1901 it was discovered that the blood of healthy people contained substances capable of causing agglutination (clumping) of erythrocytes in other individuals. Study of the agglutination of erythrocytes belonging to one person in the blood plasma or serum of another has provided the scientific basis for that important therapeutic measure, blood transfusion.

*Blood transfusions* are made after large loss of blood in certain types of poisoning (particularly when oxygen-binding capacity of haemoglobin is impaired), in conditions with a reduced haemoglobin content in the blood, and in many other circumstances. Attempts to transfuse blood frequently used to result in death, or caused severe

disorders in the body. Severe after-effects can occur when the erythrocytes of the *donor* (the individual who supplies the blood) are agglutinated by the blood plasma of the *recipient* (the individual who receives the blood), which happens when the erythrocytes of the transfused blood contain an agglutinable substance, *agglutinogen*, and the plasma of the recipient contains a corresponding agglutinant substance, *agglutinin*. Erythrocyte agglutination followed by haemolysis causes a severe body condition, *post-transfusion shock*, which may terminate in death.

Jansky and Landsteiner found two agglutinable factors in human erythrocytes, agglutinogen A and agglutinogen B, and two agglutinants in the plasma, agglutinin  $\alpha$  (anti-A) and agglutinin  $\beta$  (anti-B). Human blood never contains agglutinogen A together with agglutinin  $\alpha$  or agglutinogen B together with agglutinin  $\beta$ , so that no agglutination of its own erythrocytes occurs in the organism.

It has been established that all people can be divided into four groups according to the agglutinogen in their erythrocytes and the agglutinin in their plasma. According to the Jansky classification \*, individuals with Group I blood have no agglutinogens in the red blood cells, but their plasma contains agglutinins  $\alpha$  and  $\beta$ . Individuals with Group II blood have agglutinogen A in their erythrocytes and agglutinin  $\beta$  in the plasma.

Individuals with Group III blood have agglutinogen B in the erythrocytes and agglutinin  $\alpha$  in the plasma. Individuals with Group IV blood have agglutinogens A and B in the erythrocytes and no agglutinins in the plasma.

Designating agglutination by a plus sign (+) and its absence by a minus sign (-), we can represent the results obtained on mixing erythrocytes of an individual of one blood group with the serum of an individual of another blood group as shown in the table below.

Serum Group	Erythrocyte Group			
	I (O)	II(A)	III(B)	IV(AB)
I ( $\alpha$ and $\beta$ )	-	+	+	+
II ( $\beta$ )	-	-	+	+
III ( $\alpha$ )	-	+	-	+
IV (O)	-	-	-	-

\* In Landsteiner's classification Group O corresponds to Jansky's Group I, Group A to Group II, Group B to Group III, and Group AB to Group IV.

Blood grouping is performed by mixing a drop of blood taken from the individual being tested with standard serums containing known agglutinins. Two serums, Group I (A) and II (B), are sufficient since with them the occurrence or non-occurrence of agglutination allows us to define the blood group accurately (Fig. 7).

Determination of blood group is essential for deciding whether a blood transfusion is possible. It is sufficient to determine only the non-agglutinability of the donor's erythrocytes because the plasma of the transfused blood is diluted in the recipient's blood and does not cause agglutination of its own erythrocytes.

Individuals belonging to the Group I (0) may be given a transfusion of Group I (0) blood only. Group I (0) blood, on the other hand, can be transferred to individuals of any blood group. People with this blood group are therefore known as *universal* or *general donors*. Individuals of Group IV (AB) can be given a transfusion of blood from any of the four groups, but Group IV (AB) blood can be transfused only to individuals of Group IV (AB). Individuals of blood Group II (A) or III (B) can be given a transfusion of blood of an identical group or of Group I (0). The blood of individuals belonging to Group II (A) or III (B) can be transfused to individuals with an identical blood group or with Group IV (AB). These relationships are represented in the diagram in Fig. 8.

Blood grouping made in different countries has given the following mean indices on the distribution of people among the four groups: 40 per cent belong to Group I (0), 39 per cent to Group II (A), 15 per cent to Group III (B), and 6 per cent to group IV (AB).

There is another factor in the erythrocytes of most people (85 per cent), which was first isolated in 1940 by Landsteiner and Viner in the blood of the rhesus monkey (*Macacus rhesus*) and for that reason is called the *Rhesus factor* (Rh factor). If human blood containing this factor (*rhesus-positive blood*) is transfused to an individual without it (*rhesus-negative*), specific agglutinins and haemolysins will form in his blood. A repeated transfusion of rhesus-positive blood can then cause agglutination and severe complications (*post-transfusion shock*).

Cases of a rhesus-positive foetus developing in a rhesus-negative mother are of particular importance. The rhesus factor of the foetus passes through the placenta into the mother's blood in which specific anti-rhesus substances are produced as a result. These substances re-enter the blood of the foetus through the placenta and can give rise to severe disorders due to agglutination and lysis of its erythrocytes. The phenomenon may be responsible for certain cases of stillbirth.

The concept of blood groups has been complicated of late by the discovery of new agglutinogens. For example, group A has been found to be composed of a number of subgroups ( $A_1$ ,  $A_2$ ,  $A_3$ ,  $A_4$ , etc.). Agglutinogen  $A_2$ , as distinct from  $A_1$ , does not agglutinate in

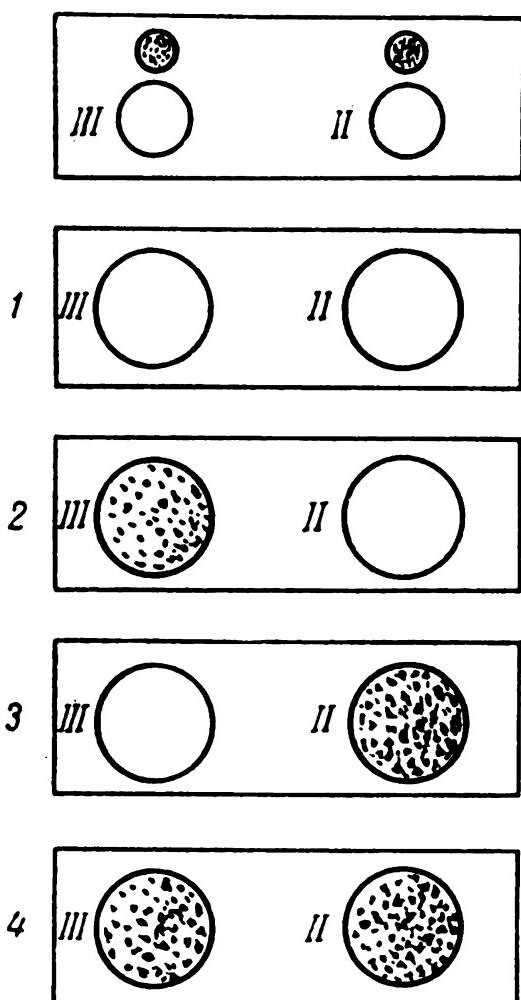


FIG. 7. Blood grouping test

Top — arrangement on the slide of two drops of the blood tested and the drops of Groups II and III sera. Roman figures designate the blood serum groups. 1 — no agglutination caused by Groups II and III sera — the blood belongs to Group I; 2 — agglutination caused by Group III serum — the blood belongs to Group II; 3 — agglutination caused by Group II serum — the blood belongs to Group III; 4 — agglutination caused both by Group II and Group III sera — the blood belongs to Group IV

poorly active serums containing agglutinin  $\alpha$ . Owing to that, the blood of these individuals may be erroneously grouped as Group I (0) blood and that can give rise to severe complications following a blood transfusion. Agglutinogens  $A_3$ ,  $A_4$ ,  $A_5$ , etc. are still weaker.

There are also three variants of the Rh factor:  $Rh^o$ ,  $Rh'$ , and  $Rh''$ . Erythrocytes devoid of the Rh factor have been found to contain an  $Hr$  factor (the reciprocal of the rhesus factor) which also has three variants:  $Hr^o$ ,  $Hr'$ , and  $Hr''$ .

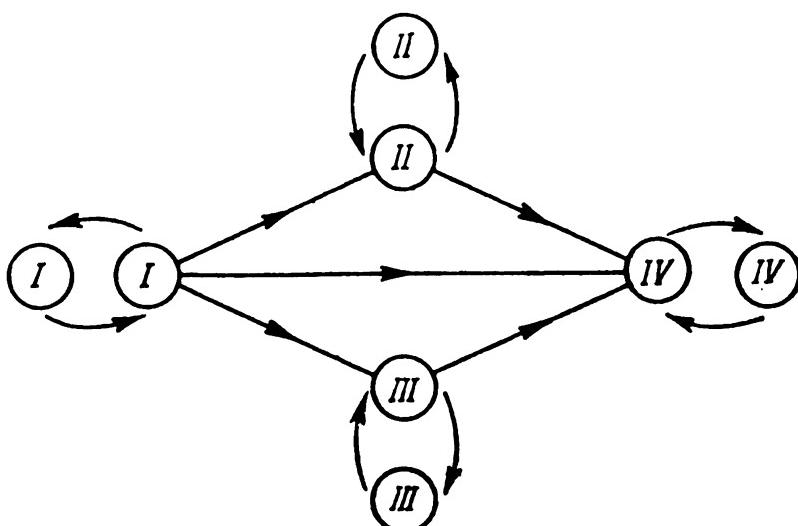


FIG. 8. Schematical representation of permissible blood transfusion. Arrows show to which recipient groups blood of a definite group may be transfused

In addition, agglutinogens M, N, S, P, D, C, K, Ln, Le, Fy, Jk, etc. have been discovered. A vast number of combinations is formed by these factors, and several hundred thousand blood groups have already been distinguished. In blood transfusion, however, grouping by the four main blood groups and the Rh and Hr factors is of the utmost importance.

#### BLOOD PLATELETS

The *blood platelets* or *plaques* are plasma elements oval or spherical in shape and two to five microns in diameter. Those present in humans and mammals have no nuclei, and for that reason most researchers consider them to be non-cellular formations. The absence of a nucleus distinguishes blood platelets from thrombocytes, typical nucleated cells present in the blood of lower vertebrates.

The number of platelets in human blood is 200,000 to 400,000 per cubic millimetre, but may vary significantly. Diurnal fluctuations are encountered; the platelet level in the peripheral blood increases in the daytime and decreases at night. That probably depends on the rhythm of work and rest; after strenuous muscular work the number of platelets in human blood increases three to five times. Platelets survive for two to five days, so that their entire number in the blood is renewed every two to five days. Blood platelets are formed by megakaryocytes, giant cells present in the red bone marrow and in the spleen.

Blood platelets are rapidly destroyed in bleeding and factors that take part in coagulation and retractozymes are liberated into the plasma (see p. 65).

On disintegration, blood platelets liberate *serotonin* (*5-hydroxy-tryptamine*), a substance that causes vasoconstriction. Thus, they counter haemorrhage not only by facilitating coagulation of the blood, but also through this vasoconstrictor, and that constitutes their defence role in the body.

#### LEUCOCYTES

*Leucocytes*, or *white blood corpuscles*, play an important role in both defence and restorative processes in the organism. Their main functions are: 1) phagocytosis, 2) production of antibodies, and 3) destruction and removal of toxins of protein origin.

The number of leucocytes is much less than the number of erythrocytes (about 0.125 to 0.16 per cent).

There are between 6,000 and 8,000 leucocytes per cubic millimetre of adult blood. An increase in their number is known as *leucocytosis*, and a decrease as *leucopenia*. Leucocytosis is characteristic of a number of pathological (inflammatory) processes, but it may also be encountered in healthy individuals (during diges-

tion of food, muscular work, in pain, and during strong emotion). For example, an increase of the leucocyte count to 11,000 has been observed in students taking a difficult examination.

Leucocytes are divided into two main groups — *granular (granulocytes)* and *agranular or non-granular (agranulocytes)* — which differ in origin and function.

*Granulocytes* (eosinophils, basophils, and neutrophils) develop from the myeloblasts of bone marrow.

*Eosinophils* form one to four per cent of the leucocyte count and stain with acid stains (eosin and others). They take part in the destruction and detoxication of toxins of protein origin and foreign proteins. Under the influence of the latter their number in the blood increases.

*Basophils* make up 0 to 1 per cent of the leucocyte count and stain with basic dyes, e. g. methylene blue and others. Their protoplasm has granules containing heparin.

The number of basophils increases during the regenerative (terminal) stage of acute inflammation, and grows slightly with chronic inflammation. It is assumed that heparin and the other products of these cells hamper coagulation of the blood in the focus of inflammation and thus facilitate resorption and healing.

*Neutrophils* (70 per cent of the total leucocyte count) stain with neutral dyes. Their main function is phagocytosis and the production of antibodies. Neutrophils accumulate in vast numbers at sites of injury to tissues and bacterial penetration. These relatively large cells are capable of active penetration of the endothelium of the capillaries and active spread in the tissues to the place where bacteria have entered. Neutrophils have an amoeboid movement due to positive chemotaxis. Their rate of movement reaches 40 microns per minute, i. e. a distance three or four-times their own diameter. Having made contact with the bacteria, neutrophils engulf, digest, and destroy them. The phenomenon was discovered by Metchnikoff and named *phagocytosis* (greek *phagein* to eat; phagocytes—cells that ingest.)

One leucocyte may engulf 15 to 20 bacteria, but having done so, it may itself die (in that case the bacteria inside it continue to multiply).

As well as liberating proteolytic enzymes that digest bacteria, neutrophils secrete a number of substances (*antibodies*) that render bacteria harmless and facilitate phagocytosis. Neutrophils ingest both live and dead bacteria, disintegrating cells of the organism itself, and foreign particles. Figuratively speaking, they are the “scavengers” of the body. The neutrophil blood count increases markedly in acute inflammatory processes.

Normally, blood contains a definite number of mature polymorphonuclear leucocytes (neutrophilic) and of their precursors, immature *stabnuclear cells* (3 to 5 per cent) and juvenile forms (0 to 1

per cent.) In neutrophilic leucocytosis the number of these immature forms increases, and *myelocytes*, from which the juvenile cells derive, may be encountered in the blood.

The *agranulocytes* include monocytes and lymphocytes (large and small).

*Monocytes* make up 4 to 8 per cent of the leucocyte count. They are thought to originate in the bone marrow, lymph nodes, and connective tissue. Arriving at a site of inflammation from the blood, they are transformed into *macrophages* (giant phagocytes).

It should be mentioned here that an accumulation of incompletely oxidized products at a focus of inflammation brings about an acid reaction which inactivates neutrophils. Macrophages differ from them in requiring an acid medium for their phagocytic and digestive activity. When inflammation develops they take the place of neutrophils.

*Lymphocytes* (21 to 35 per cent of the leucocyte count) develop mainly in the lymph nodes, but partly in the spleen, thymus, and mucous membranes. They are the most plastic of all the blood cells, and can change into monocytes and macrophages or into tissue histiocytes and connective tissue fibroblasts. These cells participate in the restorative, or reparative, processes following inflammation.

#### IMMUNITY AND IMMUNE BODIES

Defence of the organism against infections is not solely provided by phagocytosis, but is also due to humoral factors, i. e. by substances formed in the cells that render bacteria and the products of their activity harmless. In certain illnesses, caused by bacteria (infectious diseases), for example, substances (*antitoxins*) are produced and accumulated in the body that neutralize (probably by chemical binding) the bacterial poisons, or *toxins*. Repeated introduction of toxins into the blood of animals leads to the accumulation of corresponding antitoxins in it. The blood serum of these animals is used in treatment.

During many infectious diseases (e. g., during measles, smallpox, typhus, etc.) substances known as *antibodies*, or *immune bodies*, that inhibit bacterial development are produced in the body. Consequently, some diseases rarely recur in the same person. The serum of the once-infected person suppresses the causative agents of the disease. This condition of insusceptibility to diseases, due to the presence in the blood and tissues of substances that inhibit development of the infection and owing to a change in the ability of the body cells to react against the causative agent, is called *immunity*. Antibodies are produced by the leucocytes and by the cells of the reticulo-endothelial system.

The formation of immune bodies is stimulated not only by bacteria, but also in response to the parietal introduction (not by way

of the digestive tract) of any foreign protein into the body. Serum derived from an animal immunized against a foreign protein causes that protein to clot and precipitate in flakes. The phenomenon is known as *precipitation*, and the substances responsible for it as *precipitins*. Immune bodies also include the haemolysins, the agglutinins, etc.

When immune bodies are present in the body at birth the condition is known as *congenital* or *inherited immunity*. Accumulation of immune bodies during the individual's lifetime is called *acquired immunity*. Inherited immunity explains the insusceptibility of humans and some animal species to certain diseases. Man, for example, does not contract cattle plague. Congenital immunity can be impaired by external factors. Fowl which are normally insusceptible to anthrax, acquire the disease if exposed to chilling. Ionizing irradiation also lowers body resistance to infection.

Congenital immunity is mainly due to the phagocytic capacity of the leucocytes. The spores of *B.anthraxis* introduced into a rabbit are destroyed by the leucocytes, which ingest and digest them; in rabbit serum (*in vitro*), however, the spores grow well.

**Anaphylaxis** is a condition produced in an organism through repeated introduction of a foreign substance of protein origin.

If a small amount of heterogenic serum (0.02 millilitre), for example, is introduced subcutaneously into the blood of a guinea pig, or into its peritoneal cavity, the first time it will have no harmful effect. But a second injection of the same serum 15 or 20 days later will produce a violent reaction and a severe condition called *anaphylactic shock*, attended with convulsions and disturbance of respiratory and cardiac function, and terminating in death within several minutes. This occurs because the first injection of the foreign protein produces exaggerated sensitivity in the animal to that protein (*sensitizing injection*). A second injection of the same protein then produces a reaction in the sensitized animal, identical with that caused by the introduction of an extremely virulent poison (*reacting injection*).

An animal that survives the reacting injection becomes desensitized, i. e. it is freed of the condition of increased sensitivity produced by the sensitizing injection. The mechanisms of the development of these conditions are complex and have not yet been fully studied.

## BLOOD FORMATION AND CONTROL OF THE BLOOD SYSTEM

### BLOOD FORMATION

The blood and the organs in which blood cells are formed (*haemopoiesis*) and destroyed form a single *blood system* (following Lang). The system includes the bone marrow, liver, spleen, and lymph nodes; in adults the organ of blood formation is the bone marrow,

but in embryos it also includes the liver. In adults, however, the liver loses that function.

Between 200,000 and 250,000 million erythrocytes are formed every 24 hours. The nucleated erythroblasts of the red bone marrow are the cells from which the non-nucleated erythrocytes originate. Haemoglobin is synthesized in their protoplasm, or to be more precise, in granules of ribosomes. In haeme synthesis, iron forming a constituent of two proteins, ferritin and siderophilin (transferrin) is apparently utilized. The erythrocytes liberated from the bone marrow into the blood contain a basophilic substance (one that stains with basic dyes). These *reticulocytes*, as they are known, are larger than mature erythrocytes. Their level in the blood of a healthy individual does not exceed one per cent. Maturation of reticulocytes, i. e. their development into mature erythrocytes, or *normocytes*, occurs within several hours, the basophilic substance disappearing from them during the process.

The number of reticulocytes in the blood indicates the intensity of erythrocyte formation in the bone marrow.

The average life of erythrocytes is 120 days. Their life-span can be determined in various ways, but the technique of labelled atoms is now used, in which labelled erythrocytes containing radioactive isotopes of chromium ( $\text{Cr}^{51}$ ) or iron ( $\text{Fe}^{59}$ ) are introduced into the blood.

The destruction of dead erythrocytes takes place continuously through haemolysis in the cells of the reticulo-endothelial system, primarily in the liver and spleen. These organs have been called "the erythrocyte graveyard".

The production of erythrocytes, or *erythropoiesis*, requires a supply in the organism of the vitamins that stimulate the process, namely, vitamin  $B_{12}$  and folic acid (pp. 303-4). The activity of the former is 1,000 times that of the latter. Vitamin  $B_{12}$ , or *cyanocobalamin*, is the *external erythropoietic factor* which is obtained by the organism from its external environment in its food. It is absorbed in the intestinal tract only in the presence of mucoprotein, the *internal erythropoietic factor*, which is excreted by the stomach glands. According to some data, the internal factor catalyses some sort of enzyme process directly associated with assimilation of vitamin  $B_{12}$ . If the internal factor is not formed in the stomach, the body receives no vitamin  $B_{12}$ , which leads to disturbance of erythropoiesis in the bone marrow.

#### CONTROL OF HAEMOPOIESIS

Normally, the number of erythrocytes produced equals the number destroyed and their total level remains surprisingly constant.

With an oxygen deficiency, whatever the cause, the erythrocyte blood count increases, but local oxygen deficiency in the bone marrow does not intensify erythropoiesis.

Experiments have shown that transfusion of plasma derived from an animal subjected to oxygen starvation stimulates erythropoiesis in a normal animal. Oxygen deficiency (resulting from anaemia, the inspiration of gaseous mixtures with a low oxygen content, prolonged stay at high altitudes, or diseases of the respiratory organs) is attended with the appearance of *erythropoietins* in the organism, substances that stimulate blood formation. These are glycoproteins of low molecular weight. They do not occur in the blood of animals after removal of kidneys, and so are considered to be produced in those organs.

Many researchers link disturbance of erythropoietin production with the development of various diseases of the blood system, such as deficient formation of erythrocytes and reduction in the number of red blood corpuscles in the blood (*anaemia*), or their intensified production and an increase in number (*polycythaemia*). After blood loss animal serum has been found to contain substances that stimulate the production of blood platelets, as well as erythropoietins; as a result of their activity, the number of platelets almost doubles within several hours after an acute blood loss. These substances have been named *thrombocytopoietins*, and their presence has been revealed in the blood plasma of healthy humans.

The intensity of leucocyte production, or *leucopoiesis*, depends mainly upon the action of certain nucleic acids and their derivatives. Substances stimulating leucopoiesis include the products of tissue disintegration arising from injury, inflammation, etc. The *adrenocorticotropic* (see p. 405) and *growth hormones* (see p. 400), both secreted by the hypophysis, cause an increase in the neutrophil count and a decrease in eosinophil count.

A number of studies have shown that the nervous system has a definite role in the stimulation of erythropoiesis. It had already been demonstrated in Botkin's laboratory in the eighties of the last century that stimulation of the nerves supplying the bone marrow caused an increase in the blood erythrocyte count of a dog. Stimulation of the sympathetic nerves leads to an increase in the number of neutrophils.

According to Chubalsky, stimulation of the vagus nerve leads to a redistribution of leucocytes; their number in the mesenterial vessels increases and in the peripheral vessels decreases. Stimulation of the sympathetic nerves has an opposite effect. Pain stimulation and emotional excitation increase the leucocyte count.

The leucocyte level of the blood in the circulatory system increases after eating at the height of gastric digestion. The phenomenon is known as *redistributive* or *digestive leucocytosis*.

Pavlov's disciples have shown that digestive leucocytosis can occur in response to a conditioned reflex.

The organs of the blood system (marrow, spleen, liver and lymph nodes) contain a large number of receptors which, when stimulated (according to Chernigovsky) produces various physiological reactions. Thus, there is a two-way connection between these organs and the nervous system; they receive signals from the central nervous system (which controls their condition) and, in turn, become the sources of reflexes that cause a change in the condition of the organ itself and of the organism as a whole.

## Chapter 4

### CIRCULATION

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The activity of the organs of the circulatory system, that is, of the heart and blood vessels, ensures a constant flow of blood in the organism. Because of its movement, the blood can perform numerous transport functions, in particular, supplying oxygen and nutrients to the tissues, and removing substances formed as the result of metabolism.

The movement of blood in the organism follows a complicated course known as the *systemic*, or *greater circulation*, and the *pulmonary or lesser*. The *systemic* circulation starts at the left ventricle of the heart, passes to the aorta, to the arteries originating from it and to all their branches, thence to the arterioles, capillaries, and the veins of the whole body, and finally to the two *venae cavae* which enter the right atrium. The pulmonary circulation begins from the right ventricle, continues along the pulmonary artery and all its branches, then along the pulmonary arterioles, capillaries, and veins, and terminates in the pulmonary veins which empty into the left atrium (Plate I).

The flow of blood in the vessels is due to the work of the heart. Contraction of the ventricular myocardium ejects blood under pressure from the heart into the aorta and pulmonary arteries. The movement of the blood further along the vessels, and its return to the heart, is conditioned by its pressure in the large arteries being much higher than in the small arteries, the pressure in the latter being higher than in the capillaries, and the pressure in the capillaries being higher in turn than in the veins and atria. In this way

there is a difference in pressure all along the blood stream that determines its circulation in the vascular system, blood flowing from the vessels with higher pressure to those with lower. The gradual drop in the pressure along the blood stream (from the arteries to the capillaries and veins) is brought about by the fact that the energy imparted by the heart is utilized to overcome the resistance of the vessels to the movement of the fluid arising from friction between the fluid particles and the vascular wall and between the particles themselves.

### THE HEART

The function of the heart is rhythmic pumping of blood that it receives from the veins into the arteries. It is performed by alternate rhythmic contraction and relaxation of the muscular fibres that form the walls of the atria and ventricles. Contraction of the myocardium of these chambers is known as their *systole*, and relaxation as their *diastole*.

In normal physiological conditions systole and diastole occur in a definite coordination and constitute the *cardiac cycle*. Each cycle is considered to start with the atrial systole. The contraction begins as a wave in that part of the right atrium where the orifices of the venae cavae are, and then involves both atria, which have a common musculature. With a cardiac rhythm of 75 contractions per minute, an *atrial (auricular) systole* lasts 0.1 second. As it ends, the *ventricular systole* begins, the atria then being in a state of a diastole which lasts 0.7 second. The contraction of the two ventricles occurs simultaneously, and their systole persists for about 0.3 second. After that, *ventricular diastole* begins and lasts about 0.5 second. One-tenth second before the end of the ventricular diastole a new atrial systole occurs, and a new cycle of cardiac activity begins.

The interconnection and sequence of the atrial and ventricular contractions depend upon where stimulation arises in the heart and how it spreads.

### INITIATION AND CONDUCTION OF IMPULSE

The impulses which are responsible for cardiac contraction in mammals initiate at the orifices of the venae cavae, the site of the *sinu-atrial node* described by Keith and Flack and often called after them. The node is part of the *conducting system* of the heart and is made up of poorly-differentiated muscle fibres close in structure to the embryonic and similar in morphology to Purkinje's fibres encountered in the ventricles. Similar atypical muscle fibres are scattered in the area of the atria adjacent to the sinu-atrial node and invaded by its branchings. A great number of nerve cells,

nerve fibres, and their endings, which form a ganglionic network, also occur around the node.

It has been demonstrated in various ways that stimulation arises initially in the sinu-atrial node. Extremely convincing results have been obtained with electrophysiological techniques. Changes in electrical potential have been registered by means of fine electrodes applied to different parts of the heart, and in that way it has been found that the electrical changes, which are a peculiar feature of the process of stimulation, arise initially in the sinu-atrial node and then spread to other parts of the atria and to the ventricles.

Further evidence of the site of the initial stimulation has been obtained from experiments involving strictly localized cooling or heating of the sinu-atrial node (Gaskell's test) by applying a glass capillary within which is flowing ice-cold or warm water. Local cooling of the node leads to marked retardation of cardiac activity or even to its temporary arrest. Application of cold to other parts of the heart has no such effect. An opposite effect, acceleration of cardiac activity, is produced by strictly localized warming of the sinu-atrial node.

A third proof of the fact discussed is furnished when that region of the heart suffers local damage or poisoning from certain toxic substances which may either severely retard cardiac contractions or cause cardiac arrest.

Distinct results are obtained when a ligature is placed between the venous sinus and the atria in a frog, i. e. when these structures are separated by ligation. The experiment, first made by Stannius, consists in tying a ligature round a frog's heart between the sinus and atria (ligature of Stannius); the sinus maintains its former rhythm, but the contraction of the atria and ventricles ceases since the ligature blocks the passage of impulses initiating in the venous sinus.

These experiments provide evidence that the sinu-atrial node is the *pacemaker of the heart*, i. e. that focus where the impulse responsible for cardiac contraction initiates. The wave of excitation from the node passes first to the muscle fibres of the right atrium and then to those of the left. Spreading along the muscles of the atria, it reaches the atrioventricular node which is the part of the cardiac conducting system (Fig. 9) that conveys stimuli from the atria to the myocardium of the ventricles.

The *atrioventricular node* is located in the right atrium, in the interatrial septum near the fibrous ring that separates the right atrium from the ventricle. It gives rise to the *bundle of His*, a muscular bridge that conducts stimulation from the atria to the ventricles. On entering the ventricle along the interventricular septum, the initial portion of the bundle (known as the *common branch of the bundle of His*) divides into two branches (the *right*

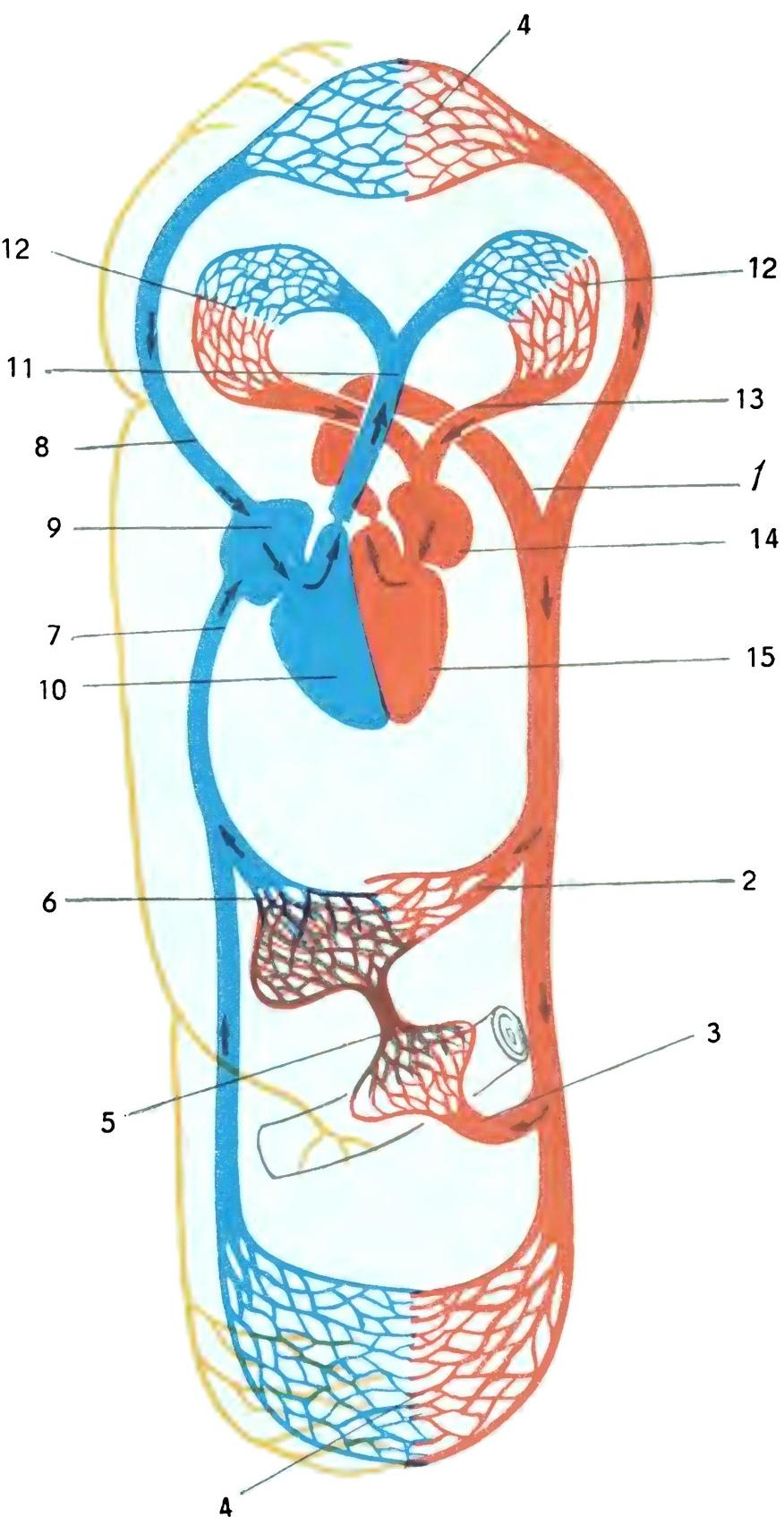


Plate I. Schematical representation of circulation in man

1 — aorta; 2 — hepatic artery; 3 — intestinal artery; 4 — capillary network of systemic circulation; 5 — portal vein; 6 — hepatic vein; 7 — inferior vena cava; 8 — superior vena cava; 9 — right atrium; 10 — right ventricle; 11 — pulmonary artery; 12 — capillary network of pulmonary circulation; 13 — pulmonary vein; 14 — left atrium; 15 — left ventricle.  
The lymphatic vessels are shown yellow

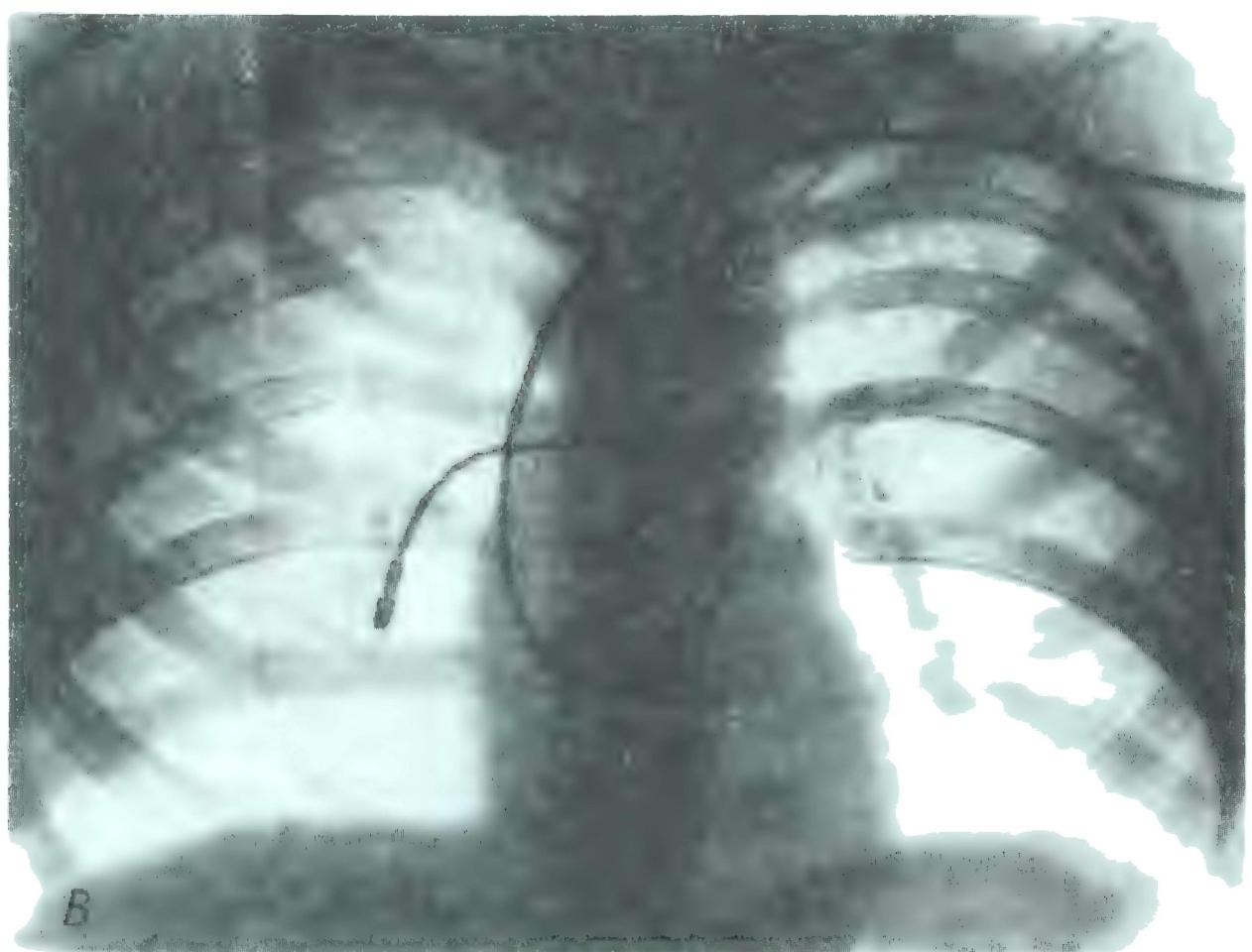
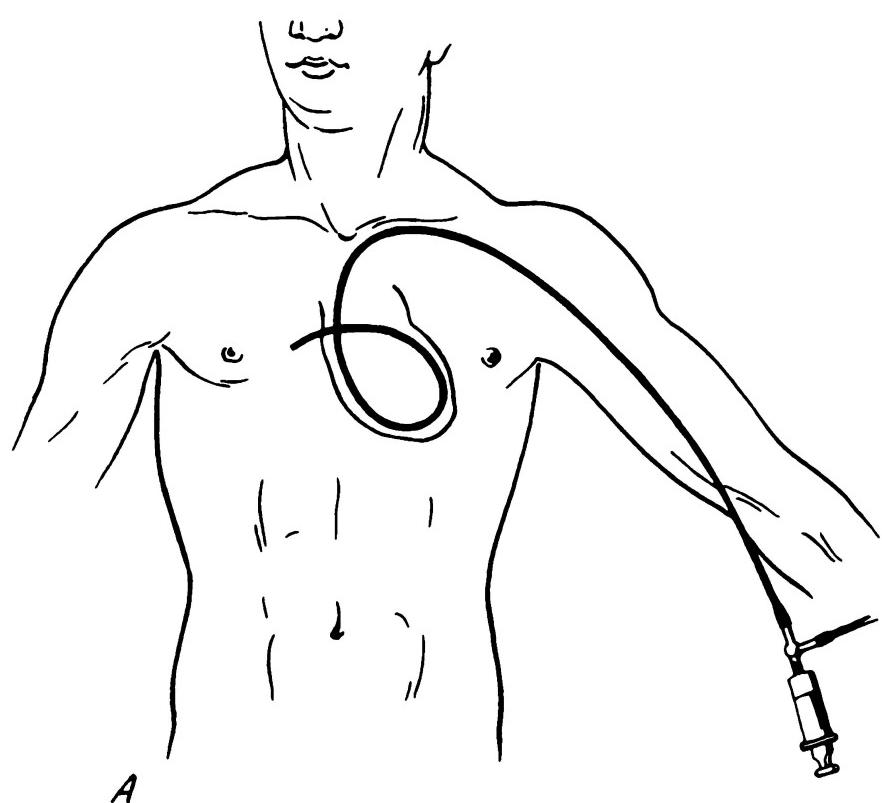
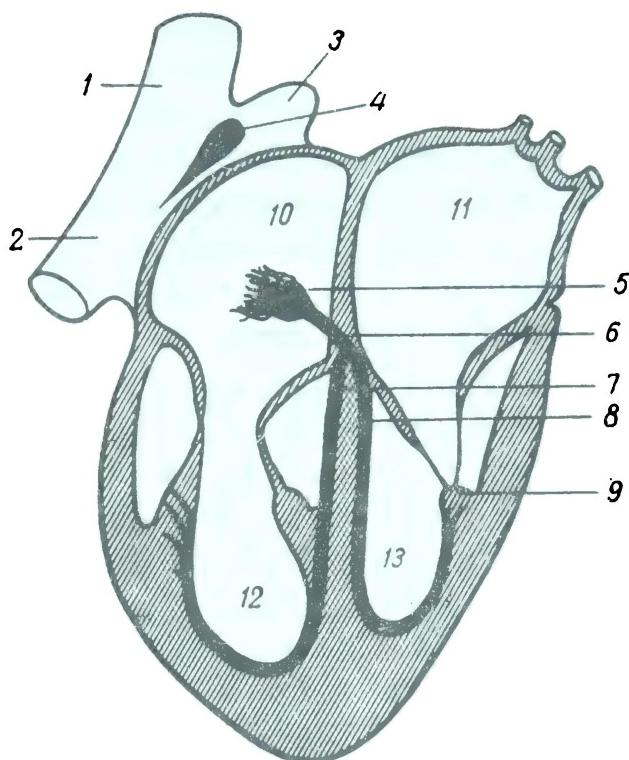


Plate II. Passage of the catheter from the ulnar vein into the right heart and pulmonary artery (A), and chest X-ray of a subject with a catheter introduced into the pulmonary artery (B) (after E. Meshalkin)



**FIG. 9. Structure of the conducting system of the heart (schematic representation)**

1 — superior vena cava; 2 — inferior vena cava; 3 — appendix of right atrium; 4 — sinu-atrial node; 5 — atrioventricular node; 6 — common branch of the bundle of His; 7 and 8 — right and left branches of bundle of His; 9 — papillary muscles; 10 and 11 — right and left atria; 12 and 13 — right and left ventricles

and *left branches of the bundle of His*), one of which passes into the right ventricle and the other into the left.

The terminal branches of the conducting system are represented by a network of Purkinje's fibres widely distributed in the subendocardial tissue that form anastomoses with the muscle fibres of the myocardium. The impulse passes along all the branches of the conducting system, reaching the whole of the myocardium and causing it to contract.

Thus the impulse responsible for cardiac contraction arises in the sinu-atrial node, spreads along the contractile myocardium of the right and left atria, and reaches the atrioventricular node. From there it passes along the bundle of His to the right and left ventricles and causes their systolic contraction.

#### PACEMAKER ACTIVITY OF THE HEART

Pacemaker activity or automatism is one of the characteristic properties of the heart. The term designates the capacity of an organ, tissue, or cell to be excited by impulses originating intrinsically without an external stimulus. Automatism is caused by changes in the metabolism of the cell.

**An isolated heart.** Automatism can most easily be studied in experiments on an isolated frog's heart which will continue to contract for hours, and even days, after being removed from the body when placed in Ringer's solution.

Contraction of the isolated heart of a warm-blooded animal can be maintained by employing *Langendorff technique*. A cannula is

introduced into the central end of the aorta of the isolated heart after being connected to a glass jar positioned higher than the heart and the vessels of the heart are perfused with Locke's or Tyrode's solution (the solution is saturated with oxygen and heated to 37° or 38°C). Under the pressure of the fluid flowing into the aorta from the jar, the semilunar aortic valves close, and the solution flows into the coronary arteries that supply the heart with nutrients. Under such conditions it can work rhythmically for hours.

The contractions of an arrested heart, animal or human, can be restored several hours after death by means of passing a solution through the vessels of the organ (*perfusion*). Experiments to resuscitate the heart of a child were first performed by Kulyabko in 1902. They were followed later by successful experiments aimed at restoring the function of a human adult heart removed from the body two days after death. The resuscitated heart continued to beat for more than 13 hours (Andreev).

**Automatism of the various parts of the heart.** The pacemaker of a normal heart, the sinu-atrial node, has the greatest capacity for automatism, but certain other parts also possess that property. It has been found in the fibres lying in the atria close to the sinu-atrial node which are similar in structure to those of the node itself. They are known as the latent pacemakers since they do not display this property under normal conditions but act only when the function of the principal pacemaker is impaired.

Pacemaker activity is also an inherent property of the atrioventricular node, as can be demonstrated experimentally on dogs by applying a ligature above the node. The procedure disconnects the atrial pacemakers and causes ventricular arrest; after an interval the pacemaker activity of the atrioventricular node resumes. The same phenomenon is encountered in severe cooling of the region of the sinu-atrial node; the arrested ventricle begins to contract again under the influence of impulses originating in the atrioventricular node. The contractions of the atria and ventricles may not occur then in the usual sequence, one after the other, but almost simultaneously because the stimulus from the node reaches their muscles almost at the same time (*atrioventricular or nodal rhythm of cardiac contraction*).

Ventricular contraction persists even after the atrioventricular node has been separated from the lower sections of the conducting system by ligation. The function of pacemaker is then performed by the Purkinje fibres lying in the right or left ventricle.

The sinu-atrial node is known as the *main pacemaker of the heart*, and the atrioventricular node, as the *potential or latent pacemaker*. The rate of cardiac contraction dictated by the sinu-atrial pacemaker in a person at rest averages 70 to 75 beats per minute. With atrioventricular rhythm the rate is about half as fast, while

a heart working under the automatism of lower lying pacemakers contracts even slower.

The frequency of automatically originating impulses is thought to show the degree of a pacemaker's activity. The differences in rate of stimulation generated by the various pacemakers mentioned above demonstrate that the sinu-atrial node possesses the highest degree of automatism, the atrioventricular node a lower degree, and the Purkinje fibres one still lower. Thus the further a focus of automatism is from the venous end of the heart, and the nearer to the arterial end, the less is its intensity, a dependence known as the decreasing gradient of automatism (Gaskell).

Only the sinu-atrial pacemaker functions under normal physiological conditions. The other pacemakers are then "silent", i. e. their automatism is suppressed by impulses from the higher located pacemaker which reach them at a higher rate than they are capable of generating themselves. With blockage of the sinu-atrial node (by means of a ligature, cooling, or the introduction of certain poisons), the rhythmic flow of impulses to the atrioventricular node and Purkinje's fibres ceases, and then the activity of these pacemakers is restored. The interval during which their automatism is restored is known as the *pre-automatical pause*, which may be several seconds long. *Asystolia*, i.e. arrest of cardiac contractions, is encountered during it.

Suppression of the automatism of the ventricular pacemakers by a rapid rate of stimuli can be demonstrated experimentally as follows. High-frequency electric stimuli are applied to ventricles whose contraction has been slowed through ligation in the region of the atrioventricular node. The ventricles begin to reproduce the rhythm of these stimuli and the effect is attended with suppression of ventricular pacemakers. Ventricular performance ceases as soon as the electric stimulation stops; after an interval to restore their pacemaker activity the ventricles begin to contract again.

**Anatomical substratum and nature of automatism.** In mature animals pacemaker activity is an inherent property of the fibres of the atypical muscles concentrated in the conducting system of the heart.

Rhythmic generation of impulses without the influence of any external stimulus can even be observed in an isolated cardiac cell, and is demonstrated *in vitro* in cardiac cell cultures. A piece cut off from the heart of any young animal, e.g. a young rat, is exposed to the action of digestive juices for a short time for the juices to digest the extracellular proteins, that cement the separate cells together, but not destroy the cells themselves. The separated cells are then washed with blood serum and placed in a glass dish in a thermostat at 37°C. The blood serum serving as nutrient is changed periodically. Several hours later, some of the cells, one in a hundred on average, begin to contract rhythmically at rates

between ten and 150 contractions per minute. It was possible to maintain the automatism of cells cultivated *in vitro* for a period of forty days, during which some of them will join to form networks, grow, and divide. The contraction of the separate cells in the culture may occur at different rhythms, but on becoming connected anatomically, they display a coordinated contractile activity, accepting the rhythm of the cell that contracts most rapidly. The cell possessing the highest automatism apparently suppresses the ability for automatism in the other cells. If a group of synchronously contracting cells is divided into two, each group will begin to contract at a different rate.

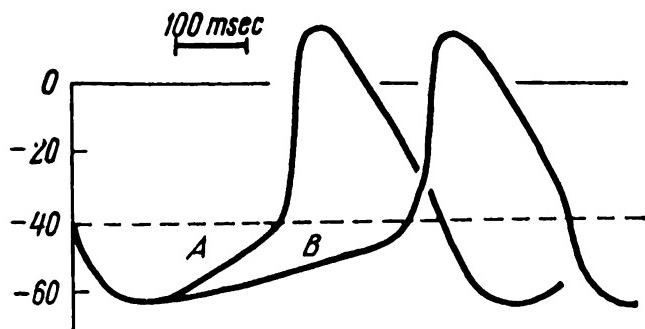
The experiments described here show that the anatomical substratum of automatism is formed by certain myocardial cells, as would be expected from the *myogenic theory of cardiac automatism*.

Electrophysiological studies employing an intracellular micro-electrode (p. 48) have revealed a feature of the pacemaker fibres, consisting in a gradual decrease of membrane potential (p. 47) (i. e. of the difference in potential between the protoplasm and the external surface of the cell) in an automatically excited cell during the pause between two contractions (diastole). A sudden sharp shift occurs in the electric charge of the cell when the membrane potential drops to a certain critical level, which is evidence of its excitation. The wave of excitation spreads to other cells, stimulating first adjacent ones and then those more remote. As a result a cell which generates impulses becomes a cardiac pacemaker. To generate a spreading excitation, membrane potential must fall by 20 or 30 millivolts. The quicker the change occurs during the diastole, the more frequently the pacemaker cell is excited, and, consequently, the more rapid the rate of contraction becomes (Fig. 10). It follows therefore that the automatism of pacemaker cells is associated with changes in their electric state.

Automatically occurring changes of intracellular potential during the diastole are characteristic of sinu-atrial node cells, several cells in different parts of the node usually becoming excited simultaneously. This means that the automatism of the node is multifocal in character. Cardiac cells not acting as pacemakers at the given time, e. g. the fibres of the atrioventricular node and Purkinje's fibres, do not show slow spontaneous changes of potential during the diastole, but if impulses from the sinu-atrial node do not reach them, the membrane of potential spontaneously falls to a level at which they become excited. Automatism is thus roused in these cells and they become cardiac pacemakers.

The cause of these rhythmical and spontaneously occurring changes in cell charge is still quite unclear. It has been suggested that acetylcholine plays a certain role in it as its content is higher in pacemaker cells than in the other cardiac muscle fibres. The cells of the sinu-atrial and atrioventricular nodes contain more

**FIG. 10.** Scheme showing the dependence of the rate of cardiac excitations upon the steepness of alterations of the pacemaker-cell membrane potential during a diastole (after Hoffman and Cranefield). The broken line indicates the critical level of the membrane potential



sodium than the contractile myocardium, which may be significant for the very important role these ions play in excitation. Automatism is evidently caused by peculiarities of metabolic processes occurring in the pacemaker cells and giving rise to changes in their surface membranes permeability.

#### PRINCIPAL PHYSIOLOGICAL PROPERTIES OF CARDIAC MUSCLE

Like other muscle, that of the heart possesses the following properties: *excitability*, or capacity to respond by excitation to a stimulus; *contractility*, or capacity to contract; and *conductivity*, or capacity to conduct excitation.

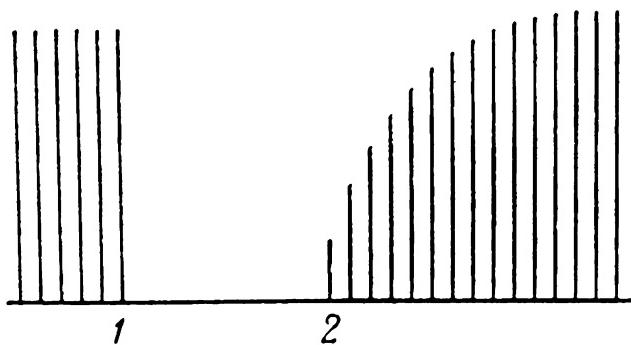
**Excitability.** Cardiac muscle can be stimulated by electrical, mechanical, thermal, and chemical stimuli, and excitation and contraction can arise in it in response to any of these.

The stimulus, however, must be equal to, or stronger than the threshold of stimulus (p. 46); one weaker will induce neither excitation nor contraction.

With a gradual increase in the strength of single stimuli the following phenomenon may be observed: the heart responds to a threshold stimulus by a contraction of maximum force. Further intensification of the stimulus brings no changes in contraction, i. e. in response to stronger stimuli the cardiac muscle contracts with the same force as to a threshold stimulus, which shows that the strength of contraction does not depend upon the strength of the stimulus, in other words, the heart either does not respond to a stimulus that is too weak, or responds by maximum contraction to one that is stronger than the threshold.

From these facts Bowditch formulated his *law of all-or-nothing*, an empirically confirmed rule that can only be applied in certain limited conditions. In fact cardiac muscle does not always respond with equal force to stimuli of different strength: the "all" varies, depending on the temperature, the extent of muscular stretching and fatigue, the composition of the nutrient solution, etc.

The inconstancy of the muscular response to excitation can be shown by experiments with a piece of muscle cut from the atrium



**FIG. 11. Bowditch's staircase phenomenon, or treppe.** A strip of myocardium prepared from a frog ventricle, that is not contracting automatically, is stimulated by rhythmical impulses

1 — cessation of stimulation; 2 — re-stimulation and the resultant treppe

or ventricle that has ceased automatic contraction. If rhythmic electric stimuli of equal strength are applied to it, the first will produce a weak contraction, the second, a stronger one, the third, a stronger one still, and so on, until a maximum force of contraction is reached. This phenomenon was also discovered by Bowditch, and is known as the *staircase phenomenon* (or *treppe*) (Fig. 11), and indicates that the law of all-or-nothing is relative and conditional as regards the heart.

The fact that cardiac contractions can be produced by electric or mechanical stimulation is of importance in medical practice. Thus, in sudden arrest of the heart or extreme deceleration of its contraction as a result of which it cannot provide an adequate supply of blood to the organs, cardiac activity may be restored or accelerated by applying rhythmical electric stimuli to the myocardium or even to the chest. Special devices, *electron stimulators*, are used as sources of the stimuli. Some diseases are treated by subcutaneous implantation of a miniature stimulator five to six centimetres in diameter supplied with a source of current capable of working for three to five years; the wires of the device, and the electrodes are sewn to the myocardium of the ventricle (Fig. 12). The heart contracts at a rate dictated by the stimulator which in this way serves as an artificial pacemaker.

Cardiac arrest is also treated by mechanical stimulation by means of rhythmic pressure applied by hand to the heart (*cardiac massage*). The procedure serves two purposes: first, cardiac contractions can be produced in response to such stimulation, and second, the rhythmic pressure exerted on the other hand forces the blood contained in the heart to enter the blood vessels and so the vital organs are supplied with the minimum amount of blood needed.

**Excitation of cardiae muscle.** The excitability of cardiac muscle cells, like that of other excitable tissue, can be judged by the changes in the electric potential difference between its stimulated and quiescent areas, or between the cell protoplasm and its external medium.

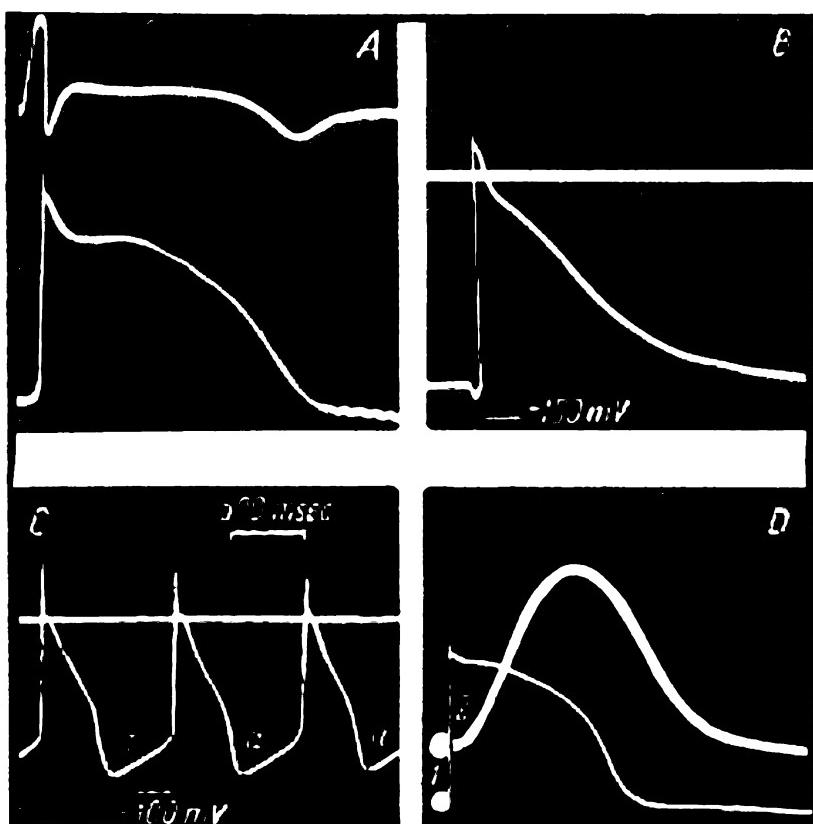
In the recent years, intracellular microelectrodes (p. 48) have been used to study the electrical manifestations of cardiac excitation.



FIG. 12. Photograph of a patient with an implanted electron cardiac pacemaker (left), and an X-ray showing the implanted pacemaker with its wires extending to the heart

At rest the protoplasm of the muscle cells is negatively charged with regard to their external surface, so that the cell membrane is *polarized*. The charge is known as the *membrane potential* and is between 80 and 90 millivolts. A sharply accelerating fall in the potential difference between cell and medium occurs at the moment of excitation. Owing to the passage of  $\text{Na}^+$  cations across the membrane into the cell, the protoplasm loses its negative charge (*is depolarized*) and even acquires a positive charge of 20 to 30 millivolts. The alteration in the potential difference during stimulation, i. e. the *action potential*, is between 100 and 120 millivolts. After that, restoration of the initial state of the cell begins, and *repolarization* of the membrane takes place. The potential difference attained during excitation is rapidly reduced, then persists at an almost constant level for a certain time, after which the membrane potential quickly reaches its initial level (Fig. 13A).

These changes in electrical state are characteristic of ventricular muscle cells. The type of action potential in other cardiac muscle cells may vary somewhat (Fig. 13B). The most pronounced differences are encountered in pacemaker cells marked by automatism, in which spontaneous depolarization occurs during a diastole (Fig. 13C).



**FIG. 13.**

A — action potential of a single ventricular muscle fibre (lower tracings) and a simultaneously recorded electrocardiogram of the entire heart (upper tracings); B — action potential of a single atrial muscle fibre; C — action potentials of the sinu-atrial node. Spontaneous depolarization (a) during a diastole may be seen (after Brooks); D — simultaneous recording of action potential (1) and contraction of a fibre (2) of a ventricular papillary muscle (after Dudel and Trautwein)

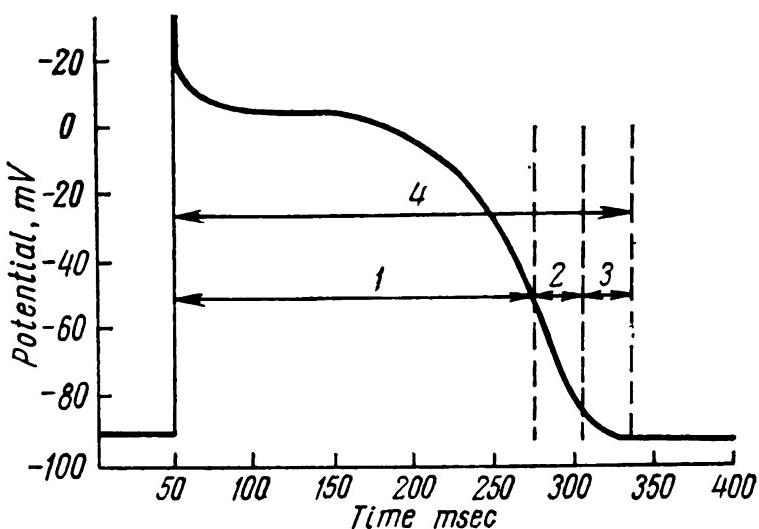
The action potential lasts longer in cardiac muscle cells than in those of skeletal muscles, having a total duration of 0.3 of a second at a rate of 70 heart beats per minute. It varies with the rate of cardiac contraction becoming shorter when the heart beats faster, and longer when it works more slowly. The sooner a wave of excitation begins after a preceding one, the shorter is its duration and, consequently, the more rapidly the action potential flows. It is that which underlies the capacity of cardiac muscle to *adopt*, i. e. reproduce, the various rhythms of excitation initiated in the sinu-atrial node. Rapid changes in the duration of the excitation wave allow quick alterations in the rhythm of cardiac contractions.

**Refractory state of the cardiac muscle.** In a state of excitation the cardiac muscle loses its ability to respond with a new wave of excitation to an artificial stimulus or an impulse from a cardiac pacemaker. This interval of inexcitability is known as the *absolute refractory period* which is a little shorter than the period of the action potential and is 0.27 of a second with a rate of 70 heart beats per minute (Fig. 14).

The refractory period of cardiac muscle persists during the entire systole produced in response to a single stimulus. For that reason, the muscle cannot respond by a continuous contraction (or tetanus) to rapidly repeated stimuli (Vol. II). With a rapid rate of excitation, cardiac muscle does not react to each successive stimulus, but responds only to every second, third, or fourth one reaching it after the refractory period has ended. So single contractions

**FIG. 14.** Correlation between changes in myocardial excitability (in response to stimulation with a cathode) and those in action potential (after Hoffmann and Cranefield).

1 — absolute refractory period; 2 — relative refractory period; 3 — supernormality period; 4 — period of complete restoration of normal excitability



separated one from another are observed. A continuous tetanic contraction of cardiac muscle has only been encountered under artificial conditions in experiments when means were used to reduce the period of refractivity markedly.

With termination of the absolute refractory period, excitability gradually returns to its initial level. This is the *relative refractory period*, which lasts 0.03 of a second. During that period myocardial excitation will only occur in response to very strong stimuli exceeding the initial threshold of stimulation.

The relative refractory period is followed by a short interval known as the *phase of supernormal excitability*, characterized by increased excitability, during which the cardiac muscle responds even to subliminal stimuli.

**Contractility of the cardiac muscle.** Excitation of the cardiac muscle causes it to contract, i. e. causes an increase in its tension, or a shortening of the muscle fibres. As with excitation, the contraction of cardiac muscle lasts longer than that of skeletal muscle produced by a single stimulus, e. g. connection or disconnection of a direct current. The contraction period of the fibres corresponds approximately to the duration of the action potential. With a rapid rhythm of cardiac activity, both the duration of the action potential and that of contraction are shortened.

Any wave of stimulation is usually accompanied by contraction, but sometimes the two phenomena can be disconnected. Thus, if Ringer's solution (p. 61) devoid of calcium salt is circulated for a long time through an isolated heart, rhythmical bursts of excitation and, consequently, action potentials continue, but contraction ceases. Experiments like that show that the presence of calcium ions is necessary for the process of contraction but not for excitation.

A break in the excitation-contraction coupling may also be encountered in a dying heart: rhythmical oscillations of electric potential still occur after contractions have already ceased.

The immediate sources of energy utilized during the first stage of contraction of cardiac or skeletal muscle are adenosine triphosphate and creatine phosphate, high-energy, phosphorus-containing compounds. Their resynthesis occurs at the expense of energy of respiratory and glycolytic phosphorylation. In cardiac muscle oxygen-utilizing aerobic processes prevail over anaerobic processes, which are much more intense in the skeletal muscles.

**Correlation between fibre length and force of contraction.** If the flow of Ringer's solution to an isolated heart is increased, i. e. if the filling of the ventricles and the stretching of their walls is intensified, the force of the contractions is augmented. The same occurs if a muscular band from a cardiac muscle is slightly stretched: the force of contraction increases as it is stretched. From facts like that it has been established that the force of contraction of the cardiac muscle fibres depends upon their initial length. This dependence underlies the "law of the heart" formulated by Starling, according to which the force of a cardiac contraction is in direct proportion to the length of the fibres during a diastole.

The law is empirical, and is only true in certain conditions.

**The mechanism and rate of impulse transmission.** Electrical phenomena are responsible for the transmission of impulses in the heart; the action potential arising in a stimulated muscle cell serves as stimulus for adjoining cells.

The amplitude of the action potential in the cells of cardiac muscle is four or five times as great as the threshold level of membrane depolarization required to generate its spread to adjoining cells. Consequently, it is far above the potential required to produce excitation in the surrounding cells. This is an important adaptational phenomenon which ensures the safety of impulse transmission along the conduction system and in the atrial and ventricular myocardium.

The rate at which the impulse is conducted varies in the different parts of the heart. In atrial myocardium of warm-blooded animals excitation spreads at a rate of 0.8 to 1.0 metre per second. In the ventricular conduction system which is composed of Purkinje's fibres the rate is higher and reaches 2.0 to 4.2 metres per second, and in the ventricular myocardium it is 0.8 to 0.9 metre per second.

A *delay* in the conduction of impulses occurs when excitation is propagated from atrial muscle fibres to the cells of the atrioventricular node. Research by Hoffman and Cranefield, employing the microelectrode technique, has shown that the spread of excitation slows down in the upper part of the atrioventricular node over a short length of one millimetre where it is at a very low rate of between 0.02 and 0.05 metre per second.

The delay in propagation of an impulse in the atrioventricular node is responsible for the fact that ventricular excitation begins after atrial, which is of great physiological importance in correlating

the work of the different parts of the heart. It is due to just this delay that excitation of the ventricles begins 0.12 to 0.18 of a second after atrial excitation has begun.

#### ELECTROCARDIOGRAPHY AS A METHOD OF STUDYING THE DYNAMICS OF EXCITATION

The generation and spread of excitation in the heart can be studied not only by recording the electric potential from single muscle cells or from the surface of the heart, but also by registering electrical changes on the body surface as a result of cardiac activity. The fact is that with the development of a difference in electric potential between the excited and non-excited areas of the heart, lines of electrical force spread over the entire body. Consequently, typical tracings reflecting the oscillations of potentials can be registered by applying electrodes to certain points on the body. This method of studying the electrical activity of the heart, introduced into practice by Einthoven, Samoilov, T. Levis, Zelenin, and others, is known as *electrocardiography*, and the tracings registered as *electrocardiograms*.

Electrocardiography is widely used in medicine as a diagnostic method for determining the character of certain disturbances of cardiac activity.

Electrocardiograms are made by means of special apparatus, *electrocardiographs*, provided with amplifiers of direct or alternating current or voltage, oscillographs, or galvanometers. The graphs are traced on moving bands of paper. An electrocardiogram is usually taken with the patient lying on his back near the instrument. Apparatus have been introduced, however, that enable electrograms to be made during active muscular work at a distance from the individual. These instruments, *telecardiographs*, are based on the principle of remote recording the electrocardiogram by radio. The electrodes on the body are connected to a small, light transmitter that is put into a pocket or fixed to a helmet worn by the person being examined (Fig. 15). Transmitter signals are received at the recording centre and reproduced as graph tracings. Electrocardiograms are made in this way on athletes during competitions and on workers performing strenuous physical work. Powerful transmitters are used to make records of astronauts during space flights.

The distribution of the lines of electrical force in the body is not uniform owing to the asymmetrical position of the heart in the chest and the peculiar shape of the human body, so that the shape of an electrocardiogram and the voltage of its peaks or waves vary with the site at which potentials are recorded.

The use of several leads from the limbs and chest has been suggested. The three most commonly used are known as *standard*



FIG. 15. Electrocardiogram recording transmitter fitted to a helmet

leads (Fig. 16), with the electrodes applied as follows: lead I to the right arm and left arm; lead II to the right arm and left leg; lead III to the left arm and left leg.

With chest leads it is advisable to put an electrode on one of the six points shown in Fig. 17. The other electrode is either placed on the right arm, or is replaced by three inter-linked electrodes applied one to each arm and to the left leg. The shape of the electrocardiogram in that case is influenced only by the electrical alterations occurring at the site of the chest electrode. The joint electrode placed on the three limbs is indifferent or neutral since its potential does not alter during the cardiac cycle. The leads were suggested by Wilson and are known as unipolar; they are designated by the letter V ( $V_1$ ,  $V_2$ , etc.).

Fig. 18 shows a normal electrocardiogram of a man made from standard leads. Various waves, designated *P*, *Q*, *R*, *S*, and *T*, are distinguished on it during each cardiac cycle. The *P* wave is caused by excitation of the atria and represents the algebraic sum of the electric potentials arising on excitation of the right and left atria. The *QRST* complex reflects the electrical alterations caused by excitation of the ventricles, the *Q*, *R*, and *S* waves characterizing the initial period of the excitation, and the *T* wave the end of the excitation. The interval between the beginning of the *P* wave and the beginning of the *Q* wave shows the time required for

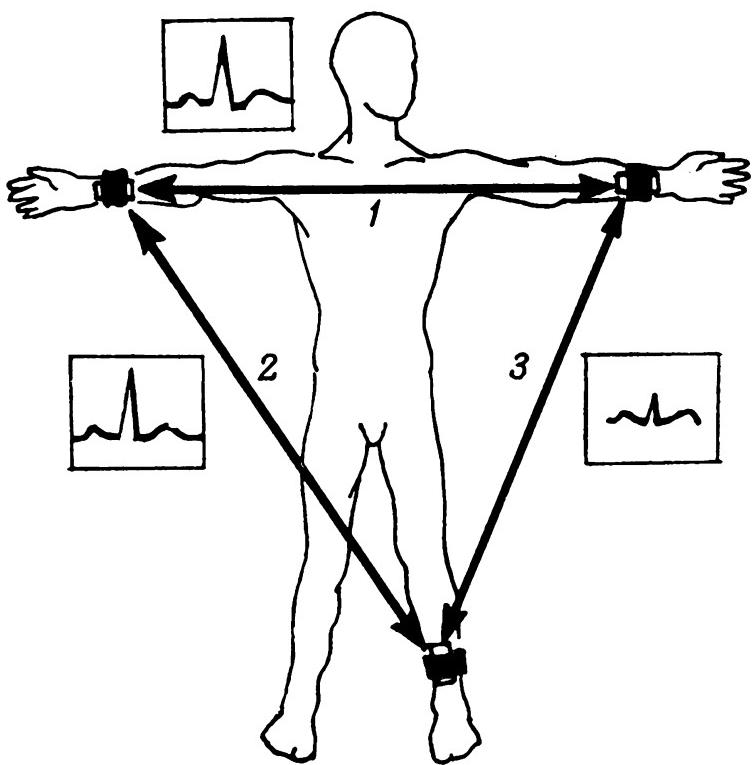


FIG. 16. Application of electrodes in standard leads used in electrocardiography, and the tracings produced

excitation to spread from the atria to the ventricles (Fig. 18). The complicated tracings of the ventricular action currents are explained by some authors as due to excitation not involving both ventricles simultaneously. The nature of the *Q*, *R*, *S*, and *T* waves is still not completely clear. It is supposed that the *Q* wave results from excitation of the internal surface of the ventricles, the right papillary muscle, and the heart apex, and the *R* wave from excitation of the surface and base of both ventricles. By the end of the *S* wave both ventricles are entirely involved in excitation and there are no potential differences between their various areas. The origin of the *T* wave is less clear. Most authors assume it to be

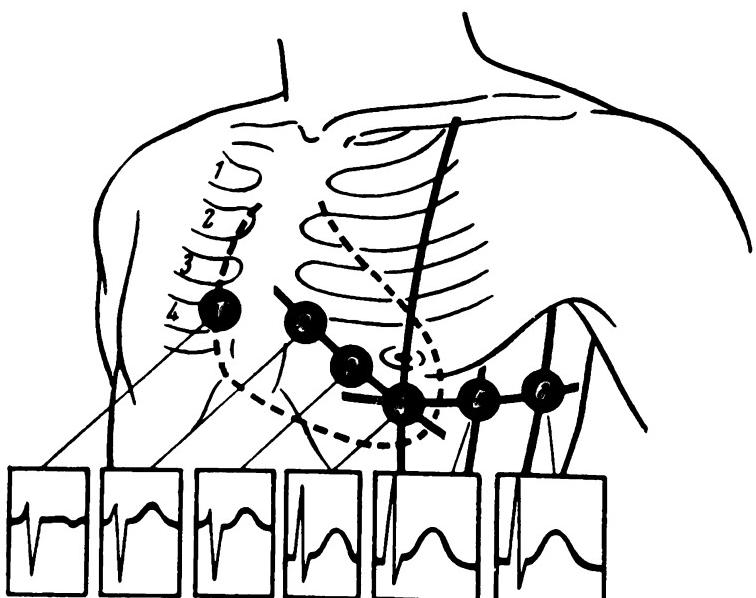


FIG. 17. Chest leads and the tracings produced

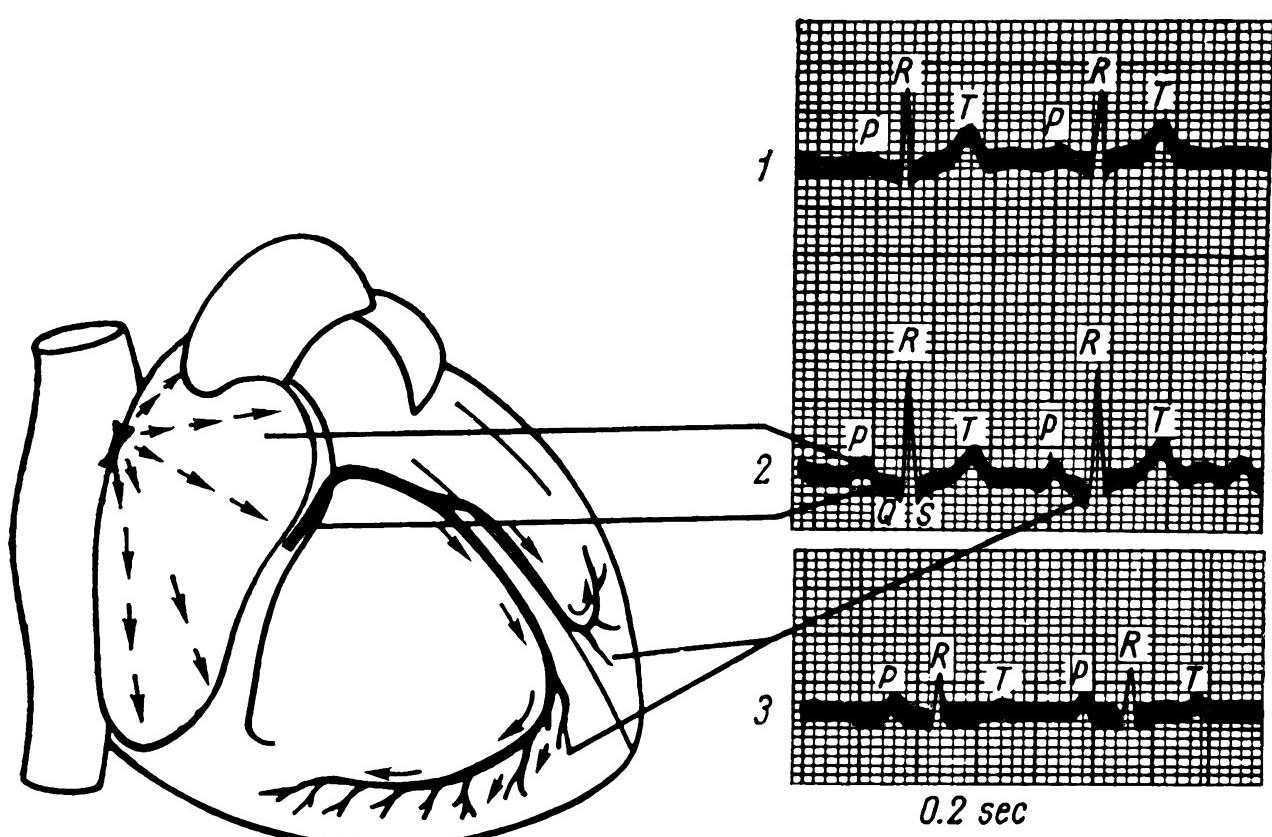


FIG. 18. Electrocardiogram made using the three standard leads, and a schematic representation of the connection existing between the spread of excitation in the heart and the appearance of certain waves on the electrocardiogram (after Bard)

associated with the final stage of repolarization, i. e. with cessation of ventricular excitation, which does not occur simultaneously in the different parts of the ventricles. This wave is the most variable ingredient of an electrocardiogram.

Zelenin has shown that the *Q*, *R*, and *S* waves are the algebraic sum of two oppositely directed electric currents arising in the right and left heart. This was later confirmed experimentally; dissection of one of the branches of the bundle of His stopped direct transmission of excitation to the corresponding ventricle, and delayed excitation of the latter occurred by an indirect route, which is reflected by marked changes in the electrocardiogram. Following dissection of the left branch of the bundle of His, for example, electrocardiograms first show excitation of the right ventricle, and then of the left.

With hypertrophy of the left ventricle, the spread of excitation along its surface is delayed somewhat compared with propagation of excitation in the right ventricle; the electrocardiogram produced then is known as a *levocardiogram*. With right ventricular hypotrophy reverse changes are encountered, and the electrocardiogram is known as a *dextrocardiogram*.

The total duration of an electrical ventricular systole, i. e. of the *Q-T* interval, nearly coincides with that of the mechanical systole (which begins a little later than the electrical).

The duration of the electrical systole ( $S$ ) depends upon the rate of cardiac activity, i. e. upon the duration of the cardiac cycle ( $C$ ); the latter is easily determined from the interval between the two  $R$  waves. The following formulae have been suggested for mathematical representation of this dependence:

$$S = 8.22 \sqrt[3]{C} \text{ (Fridericia's formula)}$$

( $C$ , hundredths of a second)

$$S = 0.37 \sqrt{C} \text{ (Bazett's formula)}$$

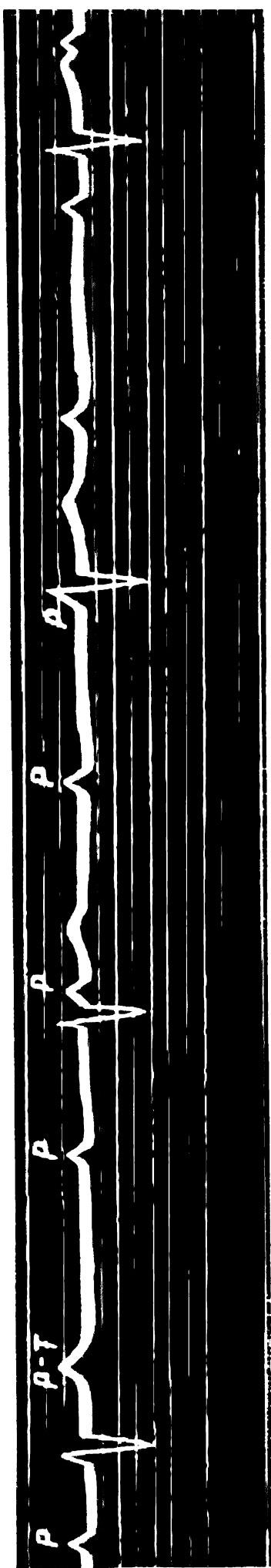
( $C$ , seconds)

Electrocardiography enables the most delicate mechanism of disturbances in the conduction of excitation in the heart to be recognized, and is indispensable for clinical examinations. The length of the interval between the beginning of the  $P$  and  $Q$  waves indicates, for example, whether or not the excitation is being conducted from the atrium to the ventricle at a normal rate. Normally the interval lasts from 0.12 to 0.18 of a second. The total duration of the  $Q$ ,  $R$ , and  $S$  waves is between 0.06 and 0.09 of a second.

**Disorders in the conduction of excitation and heart block.** Adequate correlation of atrial and ventricular contractions becomes disturbed if the conduction of excitation is impaired. The first stage of impairment is a delay in conduction. The rhythm of ventricular contractions does not change, but the electrocardiogram shows a longer interval between the  $P$  and  $Q$  waves, i. e. the conduction of impulses from the atria to the ventricles takes longer.

The second stage shows in certain impulses from the atria failing to reach the ventricles. Ventricular contraction then does not occur from time to time, e. g. every seventh or tenth beat, and some of the  $P$  waves on the electrocardiogram are not followed by the  $QRST$  complex.

With further impairment of conduction, the correlation between atrial and ventricular contraction deteriorates more and more until only every other atrial excitation reaches the ventricles. That shows on the electrocardiogram in the appearance of the  $QRST$  complex only after every second  $P$  wave. With more severe disorders the atrial-ventricular contraction ratio may reach 3:1 or 4:1, or higher. These are disturbances known as an *incomplete atrioventricular block*. Complete obstruction of impulse conduction is known as a *complete atrioventricular block*. The ventricles contract from their own pacemaker activity, and complete dissociation occurs in the rhythm of atrial and ventricular contractions. Atrial contraction occurs in the usual rhythm but the ventricles contract much more slowly because of their lower pacemaker activity. The  $P$  waves have



no definite position with regard to the ventricular *QRST* complex on the electrocardiogram and may even be superimposed on the latter at some moments. The shape of the ventricular complex is greatly changed (Fig. 19).

Heart block can be caused by various pathological conditions of the atrioventricular node and the bundle of His, e. g. impairment of blood supply in coronary sclerosis, or the presence of inflammatory foci as in rheumatic fever, etc.

Heart block can be reproduced experimentally in animals by compressing the conducting system at the site of the atrioventricular sulcus with a ligature. Sometimes impairment of conduction is encountered, not along the entire length of the bundle of His, but only along one of its branches (*bundle-branch block*). Excitation then reaches one ventricle sooner than the other, so that contraction of the first precedes that of the second.

**Changes in the cardiac rhythm.** Electrocardiography enables changes in the cardiac rhythm to be analysed in detail. The normal rate of contraction is usually between 60 and 80 per minute, but a much lower rate, *bradycardia*, may often be encountered with a frequency of 40 to 60 contractions per minute, and also a higher rate *tachycardia*, when the frequency exceeds 90 or 100, and even reaches 150 and more beats per minute. Bradycardia is often observed in athletes at rest, while tachycardia occurs during strenuous muscular work and in emotional conditions.

The rhythm of cardiac contraction is usually regular, i. e. the intervals between the separate systoles are equal in length except for cases when the rate of cardiac activity changes, that is, when one rhythm changes to another, during gradual acceleration or deceleration of cardiac activity, for example.

FIG. 19. Electrocardiogram in complete atrioventricular block (no correlation in time between the atrial P waves and the ventricular QRST complex)

In young people, however, a regular alteration of the heart rhythm in association with respiration is encountered, a phenomenon known as *respiratory arrhythmia*, which consists in decrease in the rate of contraction at the end of each expiration and the beginning of the next inspiration. The mechanism of that will be discussed later (p. 126).

A disturbance in cardiac rhythm is encountered in pathology, marked by episodic or regular appearance of a premature systole known as an *extrasystole*.

**Extrasystoles.** The occurrence of an extrasystole, and the site where the additional focus of excitation originates, can be revealed by means of an electrocardiogram. The shape of the *QRS* complex indicates whether the excitation is generated in the sinu-atrial or atrioventricular node, or in the Purkinje fibres of the right or left ventricles.

If the unusual excitation (which can be produced experimentally by applying a single electrical stimulus to the node) arises in the sinu-atrial node at the moment when the refractory period has ended but the next automatic impulse has not yet appeared, a premature heart beat, an *atrial extrasystole*, occurs (Fig. 20). The pause following it is of the same duration as a normal one.

If the irregular excitation originates in the pacemakers of the right or left ventricle it will not affect the automatism of the sinu-atrial node, which will send its next impulse at the ordinary time. The impulse will reach the ventricle when it is still in its refractory period after the extrasystole; because of that, the ventricular myocardium will not respond to the impulse from the atrium. When the refractory period ends, however, the ventricle may again respond to a stimulation but some time passes before the next impulse is conducted from the sinus. Thus an extrasystole produced by excitation originating in the ventricle itself (*ventricular extrasystole*) causes a prolonged interval, the so-called ventricular *compensatory pause*, while the rhythm of atrial performance remains unchanged (Fig. 20).

Extrasystoles may also occur with a premature excitation of the atrioventricular node; electrocardiography will show a normal shape in the ventricular *QRST* complex, but the atrial *P* wave deflection will either be inverted (directed down instead of up), or merge with the *R* wave, or, finally, may appear after the *R* wave. The character of the change in the *P* wave depends on the part of the atrioventricular node where excitation originates. The fact is that the excitation from this node spreads both to the ventricles and to the atria. If it arises in the upper part of the node, it first causes excitation of the atria and the *P* wave will precede the *QRS* complex. Excitation arising in its lower part will reach the ventricular myocardium before the atria, and the *QRS* complex will precede the

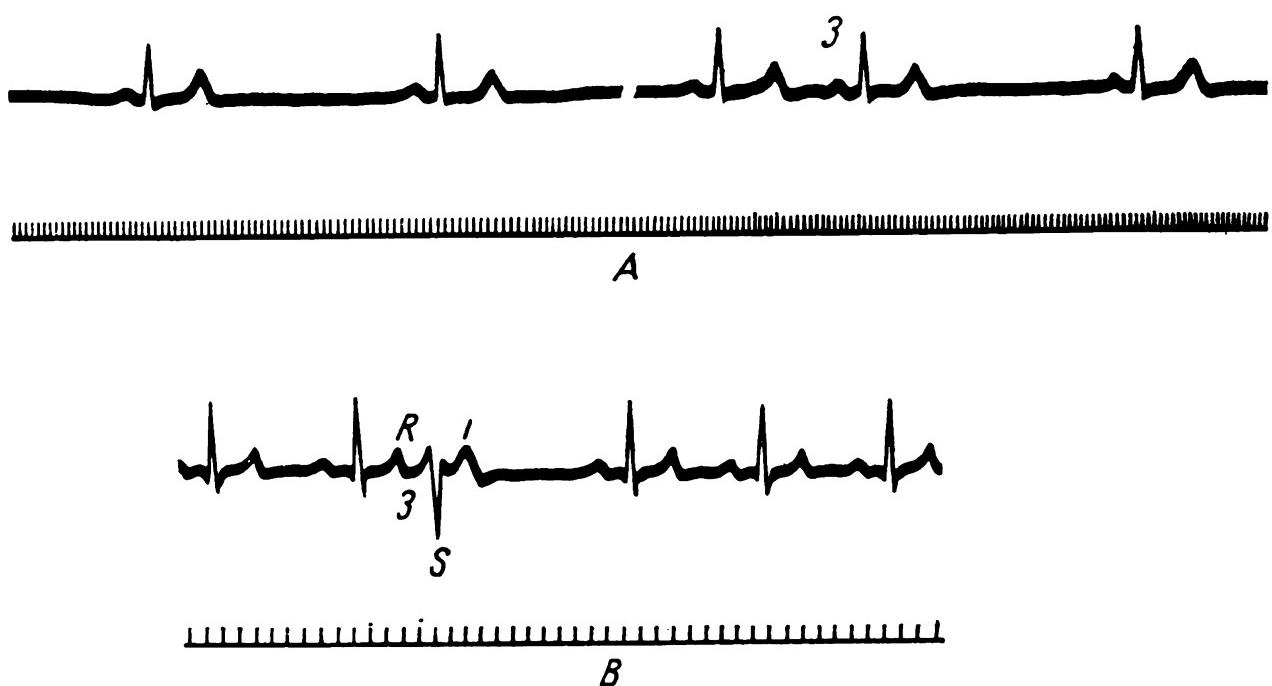


FIG 20. Atrial (A) and ventricular (B) extrasystoles

**P wave.** Excitation originating in the middle of the atrioventricular node reaches ventricles and atria simultaneously, and the *P* wave merges with the *QRS* complex.

Extrasystoles may appear in individuals due to the generation of impulses by the atrial or ventricular pacemakers. The occurrence of an extrasystole may also be facilitated by impulses transmitted to the heart from the central nervous system.

**Cardiac flutter and fibrillation.** The condition is marked by extremely rapid and asynchronous contractions of the atrial or ventricular muscular fibres, reaching a rate of 400 per minute (in flutter) or 600 per minute (in fibrillation). The principal differentiating sign of these contractions is the independent contraction of separate muscle fibres in a certain area of the heart, while the atria or ventricles contract usually as a whole. With such asynchronous contraction of their muscles, of course, the atria and ventricles can not fulfil their function of forcing blood into the vessels.

Ventricular fibrillation is fatal if appropriate measures to stop this condition are not applied. (It is most effectively arrested by a strong current of several kilovolts, an electric shock that causes simultaneous excitation of all the muscle fibres of the ventricle, followed by restoration of their synchronous contraction.) Atrial fibrillation can persist for a long time without danger to life; in the condition the rhythm of ventricular contractions is irregular because each impulse is not passed from the atria to the ventricles (Fig. 21).

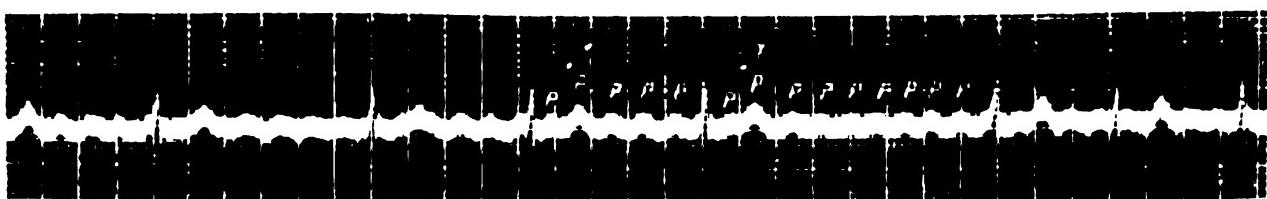


FIG. 21. Atrial fibrillation attended by ventricular arrhythmia (delirium cordis)

#### THE DYNAMICS OF CARDIAC CONTRACTION

The atria play the role of a reservoir that collects blood flowing from the veins during a ventricular systole, and from which the blood passes into the ventricles during their diastole. The ventricles act as a pump that forces blood into the arterial system at relatively high pressure.

**Movement of the blood in the heart and the role of the valves.** In normal physiological conditions, blood flows in only one direction in the heart cavities — from the atria into the ventricles, and from the ventricles into the arterial system (Fig. 22).

The ring-shaped muscle bundles of the atria which surround the orifices like a sphincter contract first during atrial systole, constricting these orifices so that blood flows from the atria only in the direction of the ventricles, and does not return into the veins. As the ventricles are relaxed during the atrial systole, and the pressure within them is lower than that in the contracting atria, blood enters them (Fig. 22,2) from the atria.

One-way passage of blood from the ventricles into the main arteries is due to *valves*: the *atrioventricular* which separate the atria from the ventricles, and the *semilunar* which separate the right ventricle from the pulmonary trunk and the left ventricle from the aorta. The opening or closing of the valves is conditioned by the height of the blood pressure on each side of them.

The atrioventricular valves, the *tricuspid* (composed of three cusps) in the right heart and the *mitral* (composed of two cusps) in the left, stop blood from returning to the atria from the contracting ventricles. They remain open during a ventricular diastole, because at that time the pressure of the blood in the ventricles is less than that in the atria. During a ventricular systole blood pressure in the ventricle increases, and the valve cusps rise above the blood and join so closely that they completely block the opening between it and the atrium (Fig. 22,3). The edges of the atrioventricular valves have tendinous cords attached at their other end to the papillary muscles of the ventricular wall. These muscles start to contract at the very beginning of the ventricular contraction and tighten these cords which prevents inversion of the valves into the atrium. The tightening of these cords is all the more necessary since the transverse size of the ventricle (from the atrioventricular septum to the apex) decreases during its systole.

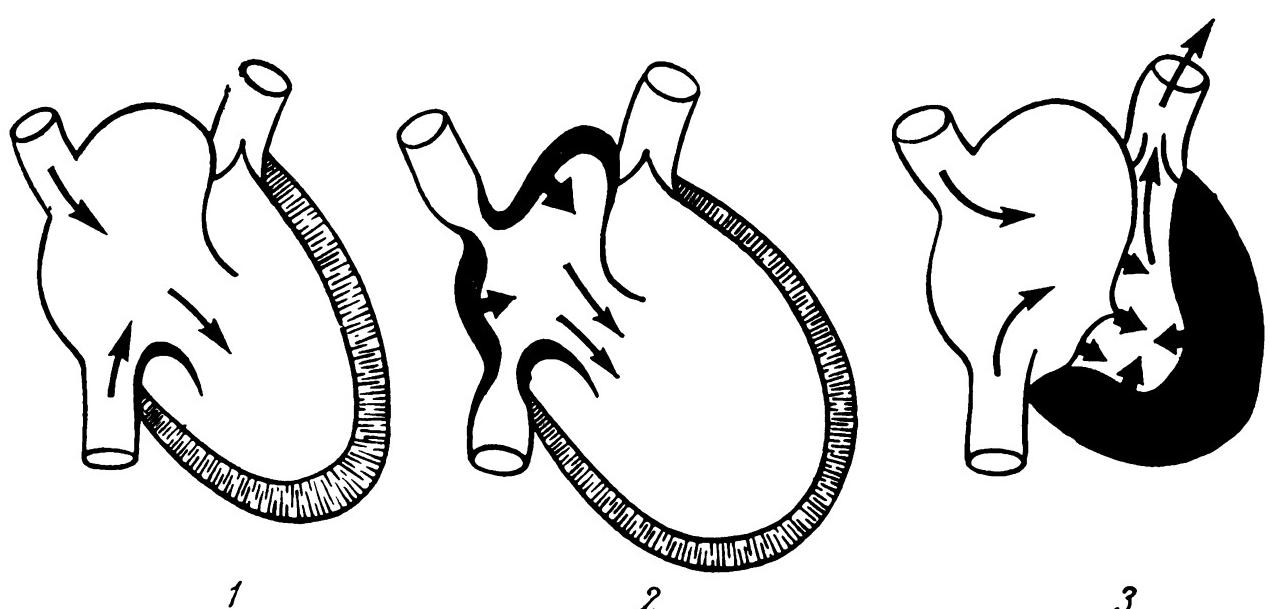


FIG. 22. Alterations in the size of the heart during different phases of the cardiac cycle (after Luisada)

1 — atrial and ventricular diastole (phase of ventricular filling); 2 — atrial systole; 3 — phase of ejection during which the blood is discharged from the ventricles

The *semilunar valves*, the *aortal* in the left heart, and the valve of the pulmonary artery in the right, prevent blood from returning to the ventricles from those arteries. During a ventricular systole blood pressure in the ventricles becomes higher than in the arterial system, and the semilunar valves open. As soon as the ventricles relax after discharging all the blood into the arteries, pressure in them becomes lower than in the aorta and pulmonary artery, and blood, flowing in the direction of the lower pressure, closes the valves (Fig. 22, 1).

**Blood pressure in the cavities of the heart, and the phases of the cardiac cycle.** As the movement of blood in the heart cavities, and along the entire cardiovascular system, is conditioned by the difference in pressure along its route, it is necessary to consider how pressure changes in the atria and ventricles during systole and diastole.

The pressure in the heart cavities and in the aorta and pulmonary artery was first measured in 1861 by Chauveau and Marey in experiments on large animals (horses and dogs). For the purpose they introduced a thin metal tube or probe connected to a pressure-recording instrument into the jugular vein, opened in the neck. The probe was advanced forward to the vena cava, and then further to the right atrium and right ventricle, and to the pulmonary artery. To determine fluctuations of pressure in the left heart, the probe was introduced into the left ventricle through the left carotid artery and the aortic arch.

Intracardiac pressure is now measured in patients suffering from certain heart diseases, when it is needed to diagnose the

character of a lesion. The procedure is to insert a thin hollow elastic tube or a *catheter* into the central segment of an incised ulnar vein and move it forward in the direction of the vena cava and further into the right atrium, the right ventricle, or the pulmonary artery (Plate II). To introduce into the aorta or the left ventricle, it is inserted into the brachial artery. The pressure in the heart cavities and main vessels can also be measured by the *puncture* method; a hollow needle is introduced into one of the atria or the ventricles, or into the aorta or pulmonary artery, through a puncture in the chest. The introduced catheter (or needle), filled with an anticoagulant solution, is connected to a sensitive manometer with a strain-gauge, which registers fluctuations of pressure.

The pressure fluctuations in the atria are relatively slight. At the peak of their systole pressure is five to eight millimetres of mercury, drops to 0 during their diastole, and then begins to increase gradually in the middle of the ventricular systole, as the atria fill with blood from the veins (Fig. 23). Pressure drops in the atria again as soon as the ventricular systole ends and the atrioventricular valves open, as the blood in them runs into the ventricles. The atrial systole begins one-tenth of a second before the ventricular, and as a result an extra amount of blood enters the ventricles. This is of no great significance, however, since most of blood filling the ventricle has already entered it during the first phase of the ventricular diastole.

The pressure in the atria during their diastole varies with the respiratory phase and becomes negative, i. e. below atmospheric pressure, during inspiration at the beginning of a diastole. The cause of the drop in pressure is an increase in negative pressure within the chest at the height of inspiration (p. 173). The fall in the pressure in the atria at the height of inspiration increases the flow of blood to them from the veins. During expiration, the negative pressure in the chest decreases, and the pressure in the atria comes close to zero at the beginning of their diastole.

The ventricular systole begins after the atrial systole has ended. The contraction wave which gradually spreads along the myocardium does not involve the entire ventricle simultaneously; some of the fibres are contracting, which stretches those that have not yet contracted. Because of that, the shape of the ventricles changes, though the pressure in them does not. The phase of the ventricular systole during which the wave of excitation and contraction spreads along the myocardium is known as the *phase of asynchronous contraction*, or the period of changing of the shape of the ventricles; it lasts 0.05 of a second. As soon as all the ventricular muscle fibres become involved in contraction, the pressure of the blood in the ventricular cavities begins to rise, and the atrioventricular valves close as a result. The semilunar valves are also closed at this time as the pressure in the ventricles is still below that in the aorta and pul-

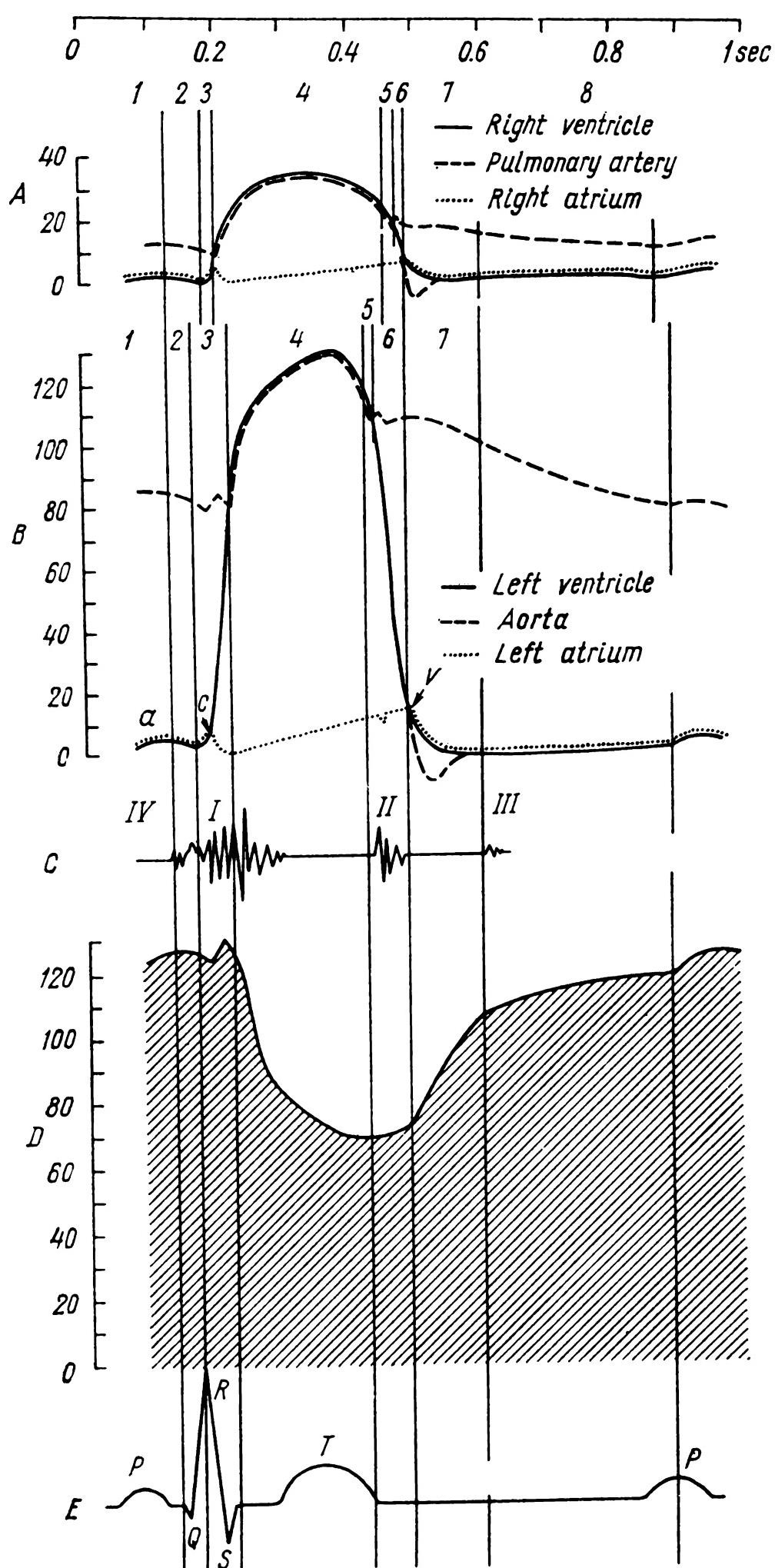


FIG. 23. Schematic representation of curves showing changes of pressure in the right (A) and left (B) heart, changes in cardiac sounds (C), changes in the volume of the ventricles (D), and the electrocardiogram (E)

monary trunk. Hence, for a short interval lasting 0.03 of a second, the ventricular muscle becomes tense but the cavities do not change in size (because the mass of blood in them, like any fluid, is practically incompressible) until the pressure in them exceeds that in the aorta and pulmonary artery and the semilunar valves open. The period of contraction occurring while the valves are closed is known as the *phase of isometric contraction* or *presphygmic period* (isometric contraction is characterized by the muscle becoming tense but not shortened). The two phases together constitute the *phase of ventricular tension* (Fig. 23, 2 and 3).

When the pressure in the ventricles exceeds that in the aorta and pulmonary trunk as a result of isometric contraction, the valves of these vessels open and the *ejection phase (sphygmic period)* during which blood is discharged from the ventricles into the vessels begins (Fig. 23, 4).

In humans discharge of blood, or *systolic ejection* into the aorta, i.e. into the systemic circulation, starts when the pressure in the left ventricle reaches 65 to 75 millimetres of mercury, while discharge into the pulmonary artery, i.e. into the pulmonary circulation, begins when pressure in the right ventricle reaches 5 to 12 millimetres of mercury.

At the beginning of the ejection phase the rise in the blood pressure within the ventricles is as steep as before the opening of the semilunar valves (the *phase of maximum ejection*, lasting 0.10 to 0.12 of a second). As the amount of blood in the ventricles decreases, the inflow of blood into the aorta and pulmonary trunk becomes less than their outflow, blood pressure ceases to increase, and by the end of the systole begins to fall (*phase of reduced ejection*, which lasts 0.10 to 0.15 of a second).

The maximum pressure level at the summit of a systole, under normal physiological conditions, is 115 to 125 millimetres of mercury in the left ventricle and 25 to 30 millimetres of mercury in the right. The greater pressure developed in the left ventricle compared with the right is due to the more powerful myocardium of the former, which is associated with the fact that the left ventricle has to overcome a greater resistance to the blood flow in the vessels of the systemic circulation. The fluctuations of pressure in the aorta and pulmonary artery during the discharge of the blood from the ventricles follow the changes of pressure in the corresponding ventricle: pressure in the aorta at the summit of the systole is 110 to 125 millimetres of mercury, and in the pulmonary artery 25 to 30 millimetres of mercury (Fig. 24).

The ejection phase is followed by the *ventricular diastole*. The ventricles start to relax, and because of this pressure in the aorta becomes higher than that in the ventricle, and the semilunar valves close. The interval between relaxation of the ventricles and closure

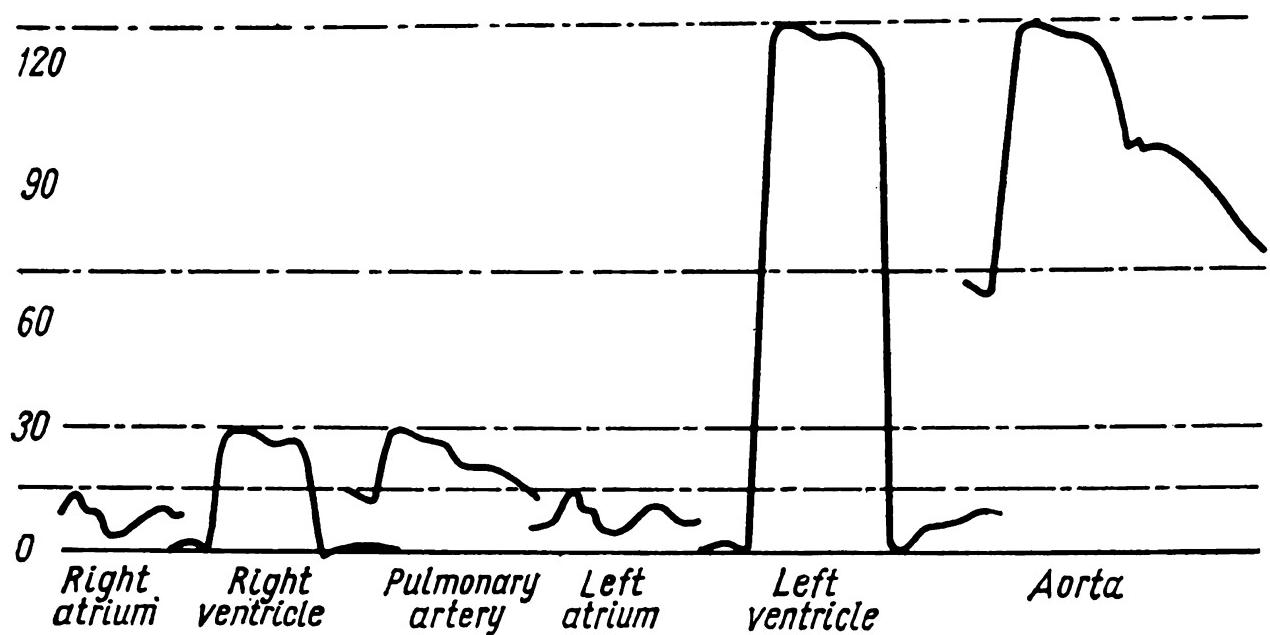


FIG. 24. Normal pressure values in the right atrium, right ventricle, pulmonary artery, left atrium, left ventricle, and aorta (after Luisada and Liu)

of the valves is known as the *protodiastolic period*; it lasts 0.04 of a second (Fig. 23, 5). Then the ventricles continue to relax for a time (about 0.08 of a second), and the atrioventricular and semilunar valves remain closed until the pressure in the ventricles falls below than that in the atria, which have now become filled with blood. This period of the ventricular diastole is designated the *phase of isometric relaxation or period of declining tension* (Fig. 23, 6); it lasts for 0.08 of a second on average. Immediately after it the cuspidate valves open, and blood from the atria flows into the ventricles.

Blood enters the ventricles rapidly at first because the pressure in them drops to zero after their relaxation (the *phase of maximum filling*, which lasts 0.08 second; Fig. 23, 7). As the ventricles fill with blood, pressure rises slightly, and the flow of blood into them becomes slower (the *phase of reduced filling*, lasting 0.16 second; Fig. 23, 8). At the end of the diastole, the atrial systole occurs, lasting 0.1 second (the *phase of ventricular filling due to the atrial systole, or the presystole*; Fig. 23, 1).

Pressure in the aorta and pulmonary artery gradually decreases during the ventricular diastole as the blood flows from them, and at the end of the diastole it drops to 65 or 75 millimetres in the aorta and to 5 or 10 millimetres of mercury in the pulmonary artery. Since this end-diastolic pressure is higher than the pressure in the ventricles, the semilunar valves remain closed until pressure in the contracting ventricles rises above that in the main arterial vessels.

The sequence of the separate phases of the cycle of ventricular activity may be represented as follows:

<b>Ventricular systole,</b> 0.33 sec	Tension phase, 0.08 sec	Phase of asynchronous contraction, 0.05 sec Phase of isometric contraction, 0.03 sec
	Ejection phase, 0.25 sec	
<b>Ventricular diastole,</b> 0.47 sec	Protodiastolic period, 0.04 sec	Phase of maximum ejection, 0.12 sec Phase of reduced ejection, 0.13 sec
	Phase of isometric relaxation, 0.08 sec	
	Phase of ventricular filling, 0.25 sec	Phase of maximum filling, 0.09 sec Phase of reduced filling, 0.16 sec
	Phase of ventricular filling due to atrial systole, the presystole, 0.1 sec	

The durations of systole and diastole, and of their phases, given here, are mean values encountered with a cardiac rate of 75 beats per minute. With a more rapid or a slower cardiac rhythm their duration changes. With acceleration of rhythm the diastole becomes much shorter, mainly through shortening of the phase of reduced filling. The shortening of the systole is relatively less, and occurs because of a decrease in the length of the phase of reduced ejection of the blood from the ventricles. With deceleration of cardiac activity, the phases of ejection and of ventricular filling change (increase in duration).

**Filling the heart with blood.** One of the factors responsible for filling the heart with blood is the residual driving force imparted to the blood by its preceding contraction. The presence of this residual force is demonstrated by the fact that blood continues to flow from the peripheral segment of the inferior vena cava dissected near to the heart, which would not be possible if the force of the previous heart contraction had been utilized completely.

A second factor causing blood to enter the heart is its aspiration (suction) by the chest, especially during inspiration. The chest is a closed airtight cavity with negative pressure owing to the elastic traction of the lungs (p.173). The cavity becomes larger during inspiration through contraction of the intercostal muscles and the diaphragm; the thoracic organs (lungs, heart, and vessels, particularly the venae cavae) are stretched, so that the pressure in the venae cavae and atria becomes negative and the blood from the periphery is vigorously aspirated into them.

Numerous facts point to the existence of a mechanism immediately responsible for the aspiration of blood into the atria. It con-

sists in the following: during the systole of the ventricles their transverse dimensions are reduced and the atrioventricular septum is pulled down, owing to which the atria are dilated and blood is aspirated into them from the venae cavae.

#### MECHANICAL AND SOUND MANIFESTATIONS OF CARDIAC ACTIVITY

The contraction of the heart is accompanied by a number of mechanical and sound manifestations that can give an idea of its dynamics when recorded.

The *apex beat* can be felt in the left fifth intercostal space, one centimetre medially of the midclavicular line, at the moment the heart contracts. The reason is as follows: the transverse dimensions of the heart alter when the ventricles contract, its ellipsoid shape changes to a round one and the density of the ventricular wall increases markedly, while the heart apex rises and presses against the chest wall. Tracings of the apex beat a *cardiogram*, are registered by means of a special instrument, the *cardiograph*, which records the fluctuations of the chest caused by the impulse.

Heart contractions can also be registered by introducing into the oesophagus a small balloon inflated with air and connected by a tube to an instrument that registers small pressure fluctuations. As the heart contracts it knocks against the oesophagus, which causes a change of air pressure within the balloon. The tracings obtained in this way, or *oesophagocardiogram*, mainly reflect the contractions of the left atrium.

Electrical registration of the motion of the cardiac silhouette on an X-ray screen, or *electrokymography*, is a very valuable method in clinical practice. A photocell connected to an oscillograph is placed on the screen at the border of the cardiac silhouette in the region of the atrium, ventricle, or aorta. The illumination of the photocell changes with the movements of the different parts of the heart, and is recorded by the oscillograph in the form of tracings.

*Ballistocardiography* has become widely used in clinical practice of late. The technique, proposed by Starr and others, is based on the fact that the ejection of blood from the ventricles, and its movement along the main vessels, produce pulsations of the entire body owing to a recoil, similar to that encountered after a gun is fired (the term ballistocardiography is formed from "ballistics", the name of the science that studies the passage of bullets or shells in a gun barrel). The pulsations of a body resulting from motion of its heart are recorded by the ballistocardiograph as tracings that have a characteristic appearance in normal conditions (Fig. 25). Tracings can be registered by means of various methods and apparatus.

Babsky and co-workers have worked out a technique for recording mechanical manifestations of human cardiac activity known as *dynamocardiography*. It is based on the fact that the motion of



**FIG. 25. Ballistocardiogram (BCG) and dynamocardiogram (DCG) recorded synchronously with an electrocardiogram (ECG), phonocardiogram (PCG), and carotid sphygmogram (SG)**

the heart (weighing about 300 grammes) in the chest, and the movement of the mass of blood from the heart into the vessels, is attended with a deviation of the centre of gravity of the chest in respect to the surface on which a person is lying. The person being examined is placed in a prone position on a special table or couch to which is fixed a device at chest level with pick-up that transform mechanical parameters into electrical. Deviations of the centre of gravity are recorded as tracings by an oscillograph. The dynamocardiogram shows all the phases of the cardiac cycle: atrial systole, the phases of ventricular tension and of ejection of blood, the protodiastolic period, the phases of ventricular relaxation and filling with blood. Electrokytmography, ballistocardiography, and dynamocardiography aid in diagnosing the disorders in cardiac activity occurring in various heart diseases.

The work of the heart is accompanied by sound phenomena known as *heart sounds*, which can be heard by pressing the ear or a stethoscope to the chest on a level with the heart. Two sounds are heard—the first at the beginning of the ventricular systole, and the second at the beginning of the ventricular diastole. The first sound is dull, prolonged, and low, while the second is short and high.

Detailed analysis of heart sounds has become possible with the use of electronic apparatus. If a sensitive microphone is connected to an amplifier and oscillograph, and pressed against the chest, heart sounds can be registered as tracings on moving film or paper. The technique is called *phonocardiography*. The tracings it gives often record two weaker heart sounds, the third and fourth, as well as the first and second sounds heard with the ear (Fig. 23).

Experiments on animals and examination of healthy individuals have shown that the first sound is mainly caused by vibrations of the stretched cusps of the atrioventricular valves and their tendinous cords. Vibrations occur during the phase of isometric contraction and at the onset of the phase of maximum ejection of blood from the ventricles. It is probable that sound phenomena associated with the contraction of the myocardial fibres also play a certain role in the origin of the first sound. Vibrations due to the opening of the semilunar valves are met at its end.

The second sound results from the closing of the semilunar valves when the pressure in the ventricles at the end of the systole becomes lower than that in the aorta and pulmonary artery. Blood trying to re-enter the heart meets the semilunar valves and slams them shut with force, causing them to vibrate.

The third sound occurs 0.11 to 0.18 of a second after the end of the second sound as the result of vibrations of the cardiac wall during maximum filling of the ventricles. The fourth sound precedes the first and is associated with vibrations of the ventricular walls during entry of the additional portion of blood at the end of the atrial systole.

In heart diseases with structural defects of the valves, when the latter do not close tightly enough (insufficiency of the valves), or when the orifice between the atrium and the ventricle, or between the ventricle and the aorta, is narrowed, normal blood flow through the heart is impaired and murmurs are heard along with the sounds; the sounds themselves also change.

#### CARDIAC OUTPUT AND STROKE VOLUME

The principal function of the heart is to discharge blood into the vascular system. For that reason, the amount of blood expelled from the ventricles is an essential index of the functional state of the heart.

The quantity of blood discharged by a ventricle per minute is known as the *minute volume or cardiac output*. It is the same, both in the right and left ventricle. The average value of cardiac output in humans at rest is 4.5 to 5.0 litres.

Dividing the cardiac output by the number of heart beats per minute, we can determine the *stroke (or systolic) volume*. With a rhythm of 70 to 75 contractions per minute, the stroke volume is 65 to 70 millilitres.

The cardiac output is measured in clinical conditions. The most precise method is that proposed by Fick, which consists in an indirect estimation of its volume from the following values: 1) the difference between the oxygen content in the arterial and venous blood; 2) the volume of oxygen utilized by the individual per minute. Let us assume that 400 millilitres of oxygen pass into the blood from the lungs per minute, and that the excess of oxygen in the arterial blood over the venous is 8 volumes per cent. That means that every 100 litres of blood absorb eight millilitres of oxygen in the lungs; to absorb all the oxygen that has entered the blood from the lungs in one minute (400 millilitres in our example), therefore, it is necessary for  $\frac{100 \cdot 400}{8} = 5,000$  millilitres of blood to pass through the lungs. That amount of blood constitutes the minute cardiac output.

Fick's method requires that mixed venous blood be derived from the right heart, because the oxygen content of the blood in the peripheral veins varies with the intensity of work performed by the body organs. At present, mixed venous blood is obtained directly from the right half of the human heart by means of a catheter introduced into the right ventricle through the brachial vein; for obvious reasons, the technique is not widely used.

A number of other methods have been elaborated to determine cardiac output and, consequently, the stroke volume. Many are based on the principle proposed by Stewart and Hamilton, which consists in determining the dilution and rate of circulation of a substance injected intravenously. Certain dyes and radioactive substances are now widely used for the purpose. After being injected into a vein, the substance passes along the right heart, the pulmonary circulation, and the left heart, and enters the arteries of the systemic circulation, where its concentration is measured. The concentration displays a wave-like change, first increasing and then decreasing. After a certain period of decrease, it again shows a slight increase (known as the *recirculation wave*), which corresponds in time to the interval during which the portion of blood containing the maximum amount of the substance passes through the left heart for the second time (Fig. 26). The time is noted from the moment the substance is introduced until the beginning of recirculation, and a *dilution curve*, i. e. a curve of the changes in concentration (increases and decreases), is constructed. Since the amount of the substance introduced into the blood and contained in the arterial blood, and the time required for it to pass along the entire cardiovascular system, are known, the cardiac output can be calculated from the formula:

$$\text{cardiac output, litres/min} = \frac{60 \cdot I}{C \cdot T}$$

where  $I$  is the amount of substance introduced, in milligrams;

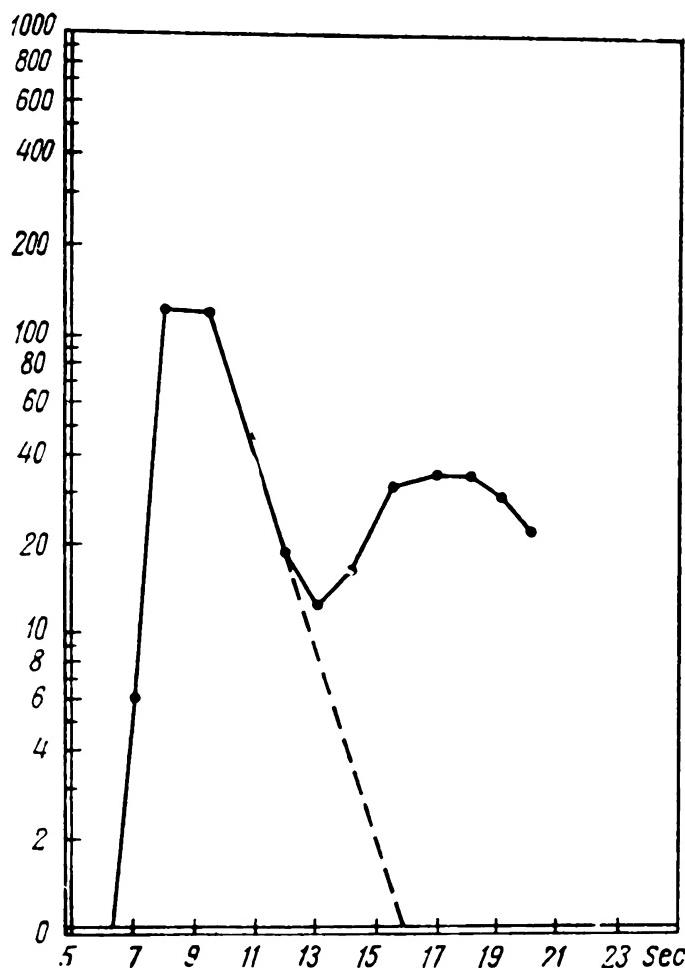


FIG. 26. Semilogarithmic concentration curve of a dye introduced intravenously

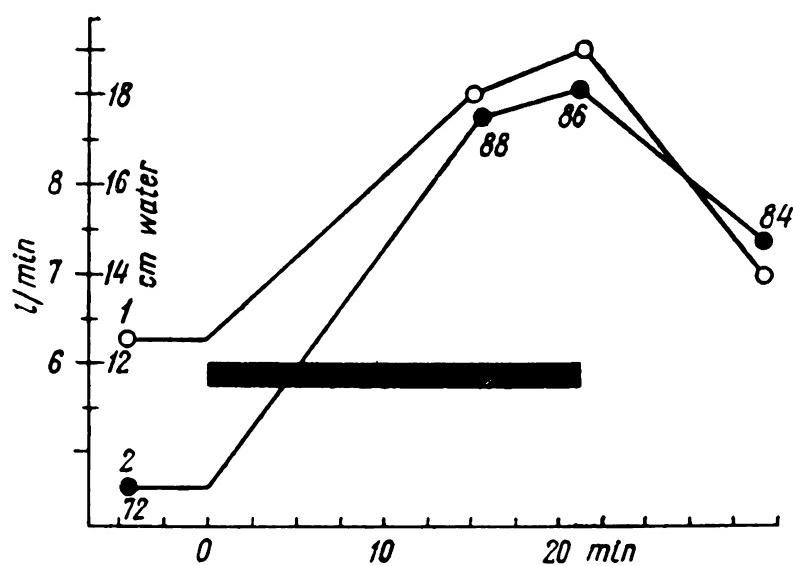
$C$  is the mean concentration, in milligrams/litre, calculated by the concentration curve;  $T$  is the duration of the first circulation wave, in seconds.

**The heart-lung preparation.** The influence of various conditions on the value of the stroke volume can be studied in an acute experiment employing the *heart-lung preparation* technique proposed by Pavlov and Chistovich, and later perfected by Starling.

This technique consists in isolating the systemic circulation by ligation of the aorta and the *venae cavae*, leaving coronary and pulmonary circulations intact. Cannulae connected to a system of glass jars and rubber tubes are introduced into the aorta and the *vena cava*. Blood expelled into the aorta by the left ventricle flows along this artificial system, enters the *venae cavae*, and then the right atrium and ventricle, and flows further through the lungs, which are rhythmically inflated by means of bellows. After passing through the pulmonary capillaries, the blood, now saturated with oxygen and rid of carbon dioxide as under normal conditions, returns to the left heart and is again directed along the artificial greater circuit.

By means of a special device it is possible to alter the resistance to the blood in the artificial circuit, and, therefore, to increase or decrease blood flow to the right atrium. In that way, the heart-lung preparation enables the load sustained by the heart to be changed at will.

**FIG. 27.** Changes in the arterial pressure (1), minute cardiac output (2), and rate of cardiac contractions (indicated by figures below the curve) occurring with an increase in the mass of circulating blood due to intravenous injection of saline solution (after Sharpey-Schafer). The thick black line shows the interval during which the solution was introduced



Experiments with the preparation enabled Starling to establish his law of the heart (p. 98). With augmentation of the diastolic filling of the heart and, consequently, with increased stretching of the myocardium, the force of cardiac contractions is intensified, so that blood flow, or in other words, stroke volume, increases. This is very important and is also observed in the cardiac activity of the intact body. If the mass of circulating blood is increased by introducing physiological solution, and blood flow to the heart is thus intensified, then both the cardiac output and stroke volumes increase (Fig. 27).

A dependence of the force of cardiac contraction and stroke volume on the diastolic filling of the ventricles and, consequently, upon the stretching of their muscle fibres, has been observed in several pathological conditions.

With insufficiency arising from a defect in the semilunar valve, blood enters the left ventricle during the diastole not only from the atrium, but also from the aorta since some of the blood ejected into it returns to the ventricle because of the valvular defect. The ventricle consequently becomes overstretched by the excess amount of blood, and the force of contraction increases correspondingly in line with Starling's law. As a result of the intensified systole a normal blood supply is maintained to the organs in spite of the defect in the valve and the return of some blood from the aorta.

**Changes in the cardiac output during work.** The stroke volume and the cardiac output are not constant values; on the contrary, they are extremely variable, and are governed by the conditions in which the organism finds itself and by the work that it performs. The cardiac output increases markedly (up to 25 or 30 litres) during muscular work, probably due to acceleration of cardiac contraction and an increase in stroke volume. An increase in cardiac output in untrained individuals occurs usually due to acceleration of heart rhythm; but in trained subjects engaged in moderate muscular

exercise an increase in stroke volume occurs and the acceleration of contraction is less marked. During strenuous work, e. g. during the immense effort required by sports competition, even well-trained athletes display an acceleration of cardiac contraction as well as an increase in stroke volume. The combination of these two phenomena results in a very big increase of cardiac output and, consequently, in an increased supply of blood to the working muscles, which provides conditions that ensure a higher working capacity. The number of heart contractions in trained individuals may exceed 200 per minute during very strenuous effort.

### CONTROL OF CARDIAC ACTIVITY

The work of the heart, and the rate and force of its contraction, varies with the activity of the organism and the various conditions in which it finds itself. Thus the body is ensured an adequate supply of blood, whatever its activity and whatever its environmental conditions. Variability of the working of the heart, and its adaptation to the requirements of the organism, are achieved by neural and humoral control mechanisms.

### THE INNERVATION OF THE HEART

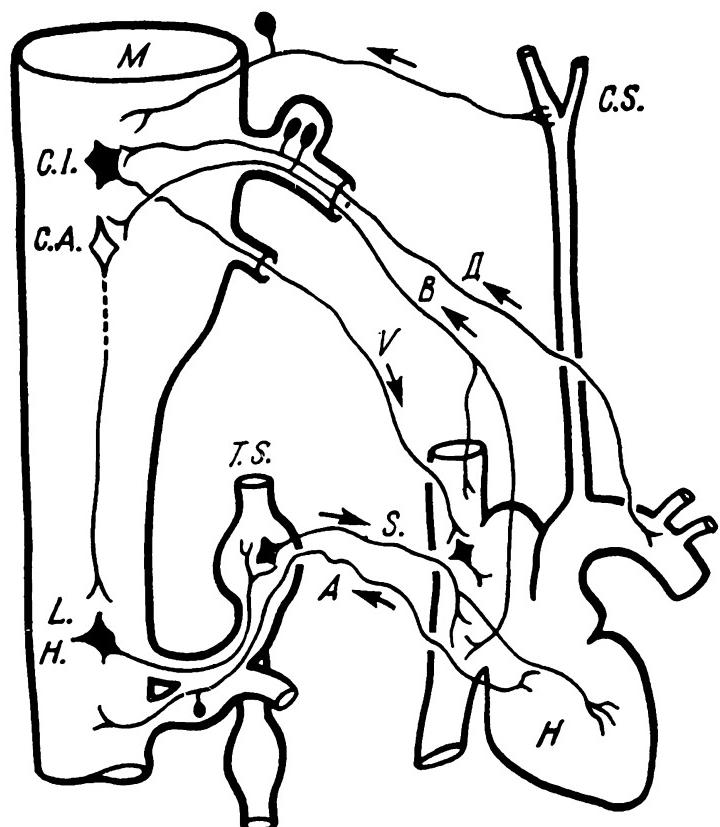
Neural control is accomplished by impulses conducted to the heart from the central nervous system along the vagus and sympathetic nerves.

Like all other autonomic nerves, the cardiac nerves are formed of two neurones. The first, whose processes form the vagus nerve, is located in the medulla oblongata (Fig. 28) and terminates in the intramural cardiac ganglia. The second neuron is located there and its processes extend to the sinu-atrial node, to the muscle fibres of the atria, and to the atrioventricular node. The cardiac ventricles are not innervated by the vagus nerve.

The first neurones of the sympathetic nervous system which transmit impulses to the heart lie in the lateral horns of the five upper thoracic segments of the spinal cord. Their processes terminate in the cervical and upper thoracic sympathetic ganglia (Fig. 28). The latter contain the second neurone, whose processes pass to the heart. Most of the sympathetic nerve fibres that innervate the heart arise from the stellate ganglion.

**The influence exerted by the vagus nerves on heart** was first demonstrated in 1845 by the Weber brothers, who revealed that stimulation of these nerves inhibited cardiac activity to the point of complete stoppage during a diastole. That was the first discovery of the inhibitory effect of the nerves in the organism.

The intensity of the effect produced by electrical stimulation of the peripheral segment of a dissected vagus nerve depends upon the



**FIG. 28. Nerve supply to the heart (schematical representation)**

H — heart; M — medulla oblongata; C.I. — centre responsible for cardiac inhibition; C.A. — centre responsible for acceleration of cardiac contractions; L.H. — lateral horn of spinal cord; T.S. — sympathetic trunk; V — efferent fibres of vagus nerve; D — depressor nerve (afferent fibres of vagus nerve); S — sympathetic fibres; A — afferent fibres of the spinal cord; C.S. — carotid sinus; B — afferent fibres from right atrium and vena cava

force of the stimulation. Weak stimulation causes deceleration of cardiac contraction, a phenomenon known as the *negative chronotropic effect* (Fig. 29). A diminution of the amplitude of cardiac contraction is encountered at the same time which is called the *negative inotropic effect*.

Strong stimulation of the vagus nerve causes temporary arrest of cardiac performance (Fig. 30). The excitability of heart muscle is reduced during stimulation of the vagus nerve, so that a stronger stimulus is required to excite it. This reduction of excitability under n. vagi is called the *negative bathmotropic effect*. Impairment of cardiac conductivity during stimulation of the vagus nerve is known as the *negative dromotropic effect*. A complete atrioventricular block frequently occurs during stimulation of the vagus nerve.

Registration of the potentials of separate heart cells by means of microelectrodes has shown that vagal stimulation causes an increase in membrane potential or hyperpolarization (Fig. 31).

The atrial refractory period diminishes under the effect of stimulation of the vagus nerve.

With prolonged stimulation of the vagus nerve, cardiac performance, at first arrested, begins again in spite of the persisting stimulation, a phenomenon known as "escape", i. e. release of the heart from the influence of the vagus nerve.

The influence of the sympathetic nerves on the heart was first studied in 1867 by Cyon and later by Pavlov. The former described an increase in the rate of cardiac performance under stimulation of the sympathetic nerves (*positive chronotropic effect*); the related fibres he

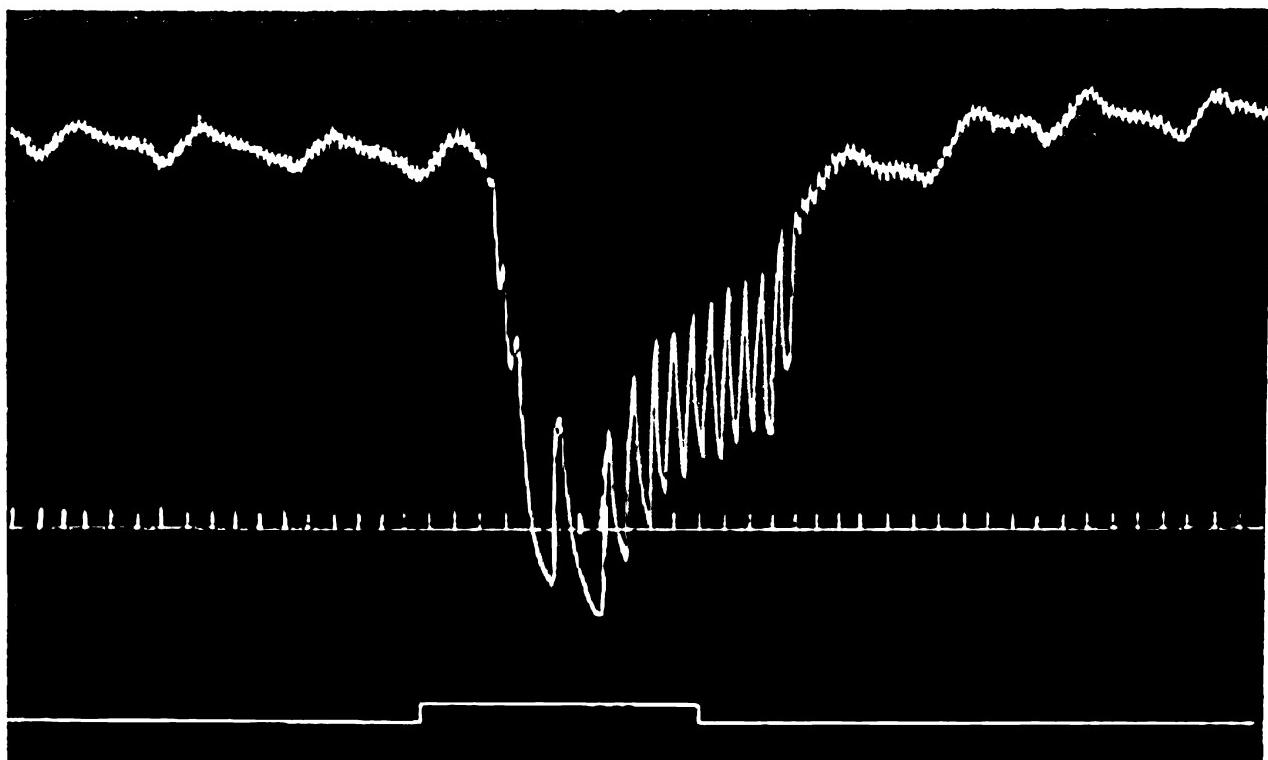


FIG. 29. The influence of stimulation of the peripheral segment of a dissected vagus nerve on the blood pressure in a dog. The time chart and the period of stimulation are shown below the blood pressure tracings

called *nn. accelerantes cordis (cardiac accelerators)*. In 1887 Pavlov revealed the presence of nerve fibres that caused intensification of cardiac contraction without marked acceleration of heart rate, i. e. that intensified cardiac activity (*positive inotropic effect*). In his view, their intensifying effect was a special trophic one, i. e., they affected the heart by stimulating metabolism.

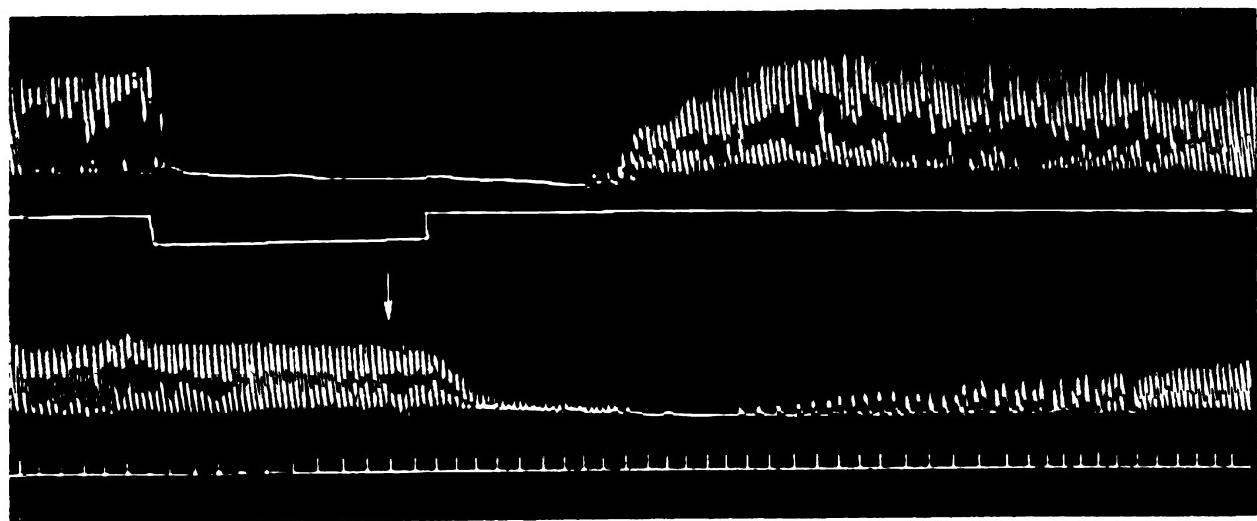


FIG. 30. Influence of vagal stimulation on a frog heart

Upper tracings record contractions of an isolated heart; the line below the tracings indicates the period of stimulation of vagus nerve supplying the heart. Lower tracings record contractions of another isolated heart. The arrow points to the moment when the nutrient fluid flowing through the first heart during its stimulation was transferred into the second heart. This also inhibited cardiac activity

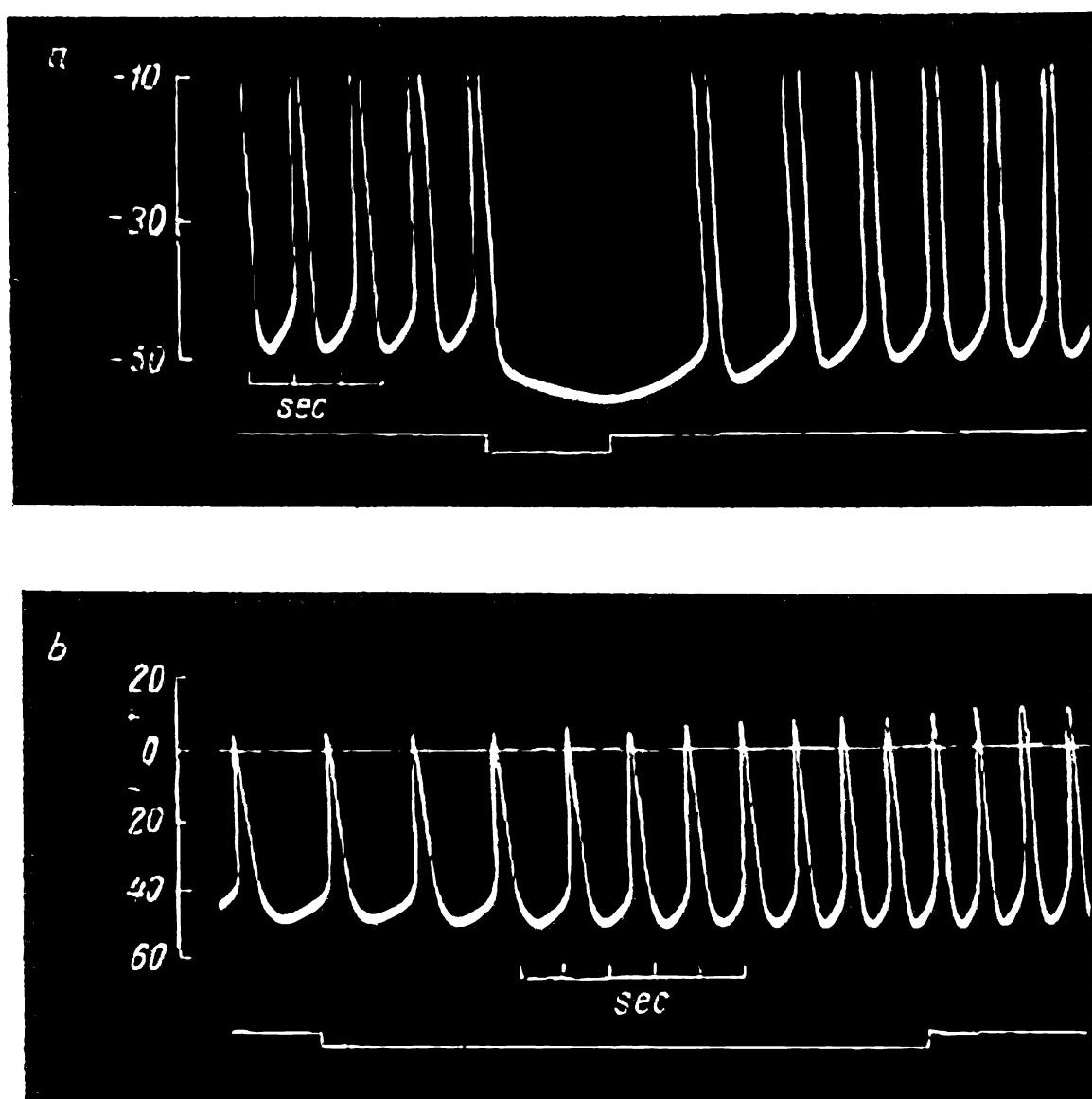
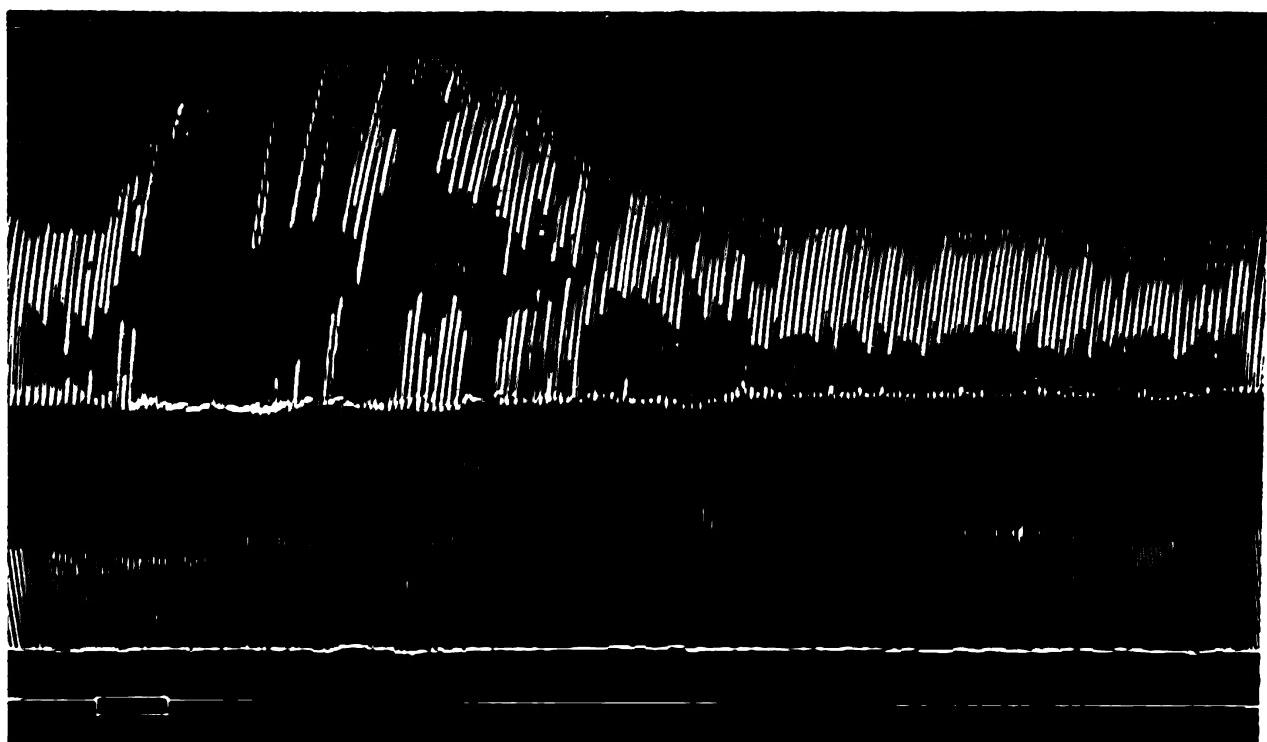


FIG. 31. Action potentials of a frog heart pacemaker-cell during stimulation of the vagus nerve (a) and the sympathetic nerve (b) (after Hutter and Trantwein)  
 (a) shows only the lower half of the action potential

Stimulation of the sympathetic nerves causes a more rapid spontaneous depolarization of the pacemaker-cells during a diastole, which leads to acceleration of heart contraction (p.92), and to an increase in the amplitude of action potentials (Fig. 31).

Stimulation of the cardiac branches of the sympathetic nerve facilitates conduction of excitation in the heart (*positive dromotropic effect*), and increases cardiac excitability (*positive bathmotropic effect*). The effect is produced after a latent period lasting ten seconds or longer, and persists long after stimulation of the nerve has ceased (Fig. 32).

The significance of the cardiac nerves in the adjustment of the organism to effort can be seen from the following observation: if the nerves responsible for innervation of a dog's heart are dissected, the pulse rate increases only by ten to twelve beats per minute during strenuous muscular activity, and the dog is able to exert mus-



**FIG. 32. The influence of sympathetic stimulation on a frog heart (after V. Boldyrev)**

The sympathetic nerve of an isolated heart is stimulated in the interval shown on the bottom line. This causes marked augmentation and acceleration of cardiac contractions (upper tracings). Sympathin (norepinephrine) appears in Ringer's solution during cardiac stimulation and when this solution is transferred into the other heart not subjected to stimulation an effect similar to that caused by stimulation of the sympathetic nerve is produced (lower tracings)

cular effort (e. g. to run) for only a few minutes (whereas it could run for several hours before the nerves were dissected).

#### CHEMICAL MECHANISM OF NERVE IMPULSE TRANSMISSION IN THE HEART

Under stimulation of the cardiac vagus nerves their endings produce *acetylcholine*, while with stimulation of the sympathetic nerves their endings produce *noradrenaline (sympathin)*. These substances are the immediate agents causing inhibition or intensification of cardiac activity, and for that reason are known as mediators (i. e. transmitters) of nerve stimulus. Their existence was demonstrated by Loewi who stimulated the vagus and sympathetic nerves of an isolated heart and then passed the fluid from that heart to another one which had not been subjected to nerve stimulation: the reaction of the second isolated heart was identical to that produced in response to stimulation of the nerves. Consequently, stimulation of the nerves of the first heart led to production of the corresponding mediator into the nutrient fluid. The effects obtained from transferring the Ringer's solution that had been in a heart during stimulation of n. vagi and n. sympathici are shown by the lower tracings in Figs. 30 and 32.

The *acetylcholine* formed in the endings of the vagus nerve is rapidly destroyed by *cholinesterase*, an enzyme present in the blood and body cells. Therefore acetylcholine has only a topical effect at its point of production. The sympathetic mediator noradrenaline is destroyed much more slowly and its effect is of a longer duration, which accounts for the fact that the acceleration and intensification of cardiac performance persists for some time after the cessation of sympathetic stimulation.

#### TONE OF CENTRES THAT CONTROL CARDIAC ACTIVITY

The nerve centres that give rise to the vagal nerves innervating the heart are in a state of constant excitation known as the *central tone*. Because of that, inhibitory impulses are continuously conducted to the heart along these nerves. In a dog cessation of their flow, following cutting of both vagus nerves, results in acceleration of heart beat.

In man the vagal effect can be temporally blocked by introduction of the alkaloid *atropine*, which increases the rate of cardiac contraction.

Removal of both stellate ganglia from which the sympathetic cardiac nerves arise causes no stable deceleration of heart beat since these nerve centres have either no tone or a very weak one.

The central tone of the vagus nerves is maintained by reflex influences, i. e. by excitation of their nuclei by impulses from various receptors along the afferent nerves. Particularly important in this respect are the afferent impulses that reach them from the receptors lying in the aortic arch and carotid sinus. Dissection of those nerves leads to a sharp drop in tone of the vagal nuclei with a resulting acceleration of cardiac contraction like that following dissection of the vagus nerves themselves.

Certain chemical factors also exert an effect on the tone of the vagus nerves. Their influence can be studied by the technique suggested by Heymans, which consists in joining the blood vessels of two dogs in such a manner that the blood of dog A flows into the head of dog B. After joining of the vessels, B's head is severed from its body with only the vagus nerves left intact. Heymans' technique makes it possible to determine precisely whether a substance introduced into the body affects the heart directly or causes changes in its activity by excitation of the vagal nuclei. Indeed, if the introduction of a substance into A's blood causes a change in the activity of B's heart, while injection of the same substance into B's blood does not, then it is obvious that the substance tested exerts its influence only through the vagal nuclei. It has been shown in this way that the tone of the nuclei of the vagus nerves increases with an increase in the blood of adrenaline secreted

by the adrenal cortex, and also with an increase of calcium ions or carbon dioxide.

The vagal tone changes with the respiratory phase, becoming higher at the end of expiration and at the beginning of the next inspiration, so that cardiac performance becomes slower. This results in *respiratory arrhythmia*, which disappears after cutting of the vagus nerves or the introduction of atropine.

A persistent increase of the tone of the vagal nuclei is sometimes encountered in human beings, manifested by *bradycardia*, i. e. deceleration of cardiac performance. The reverse phenomena, *tachycardia*, i. e. acceleration of cardiac performance, may be encountered with a fall in the vagal tone.

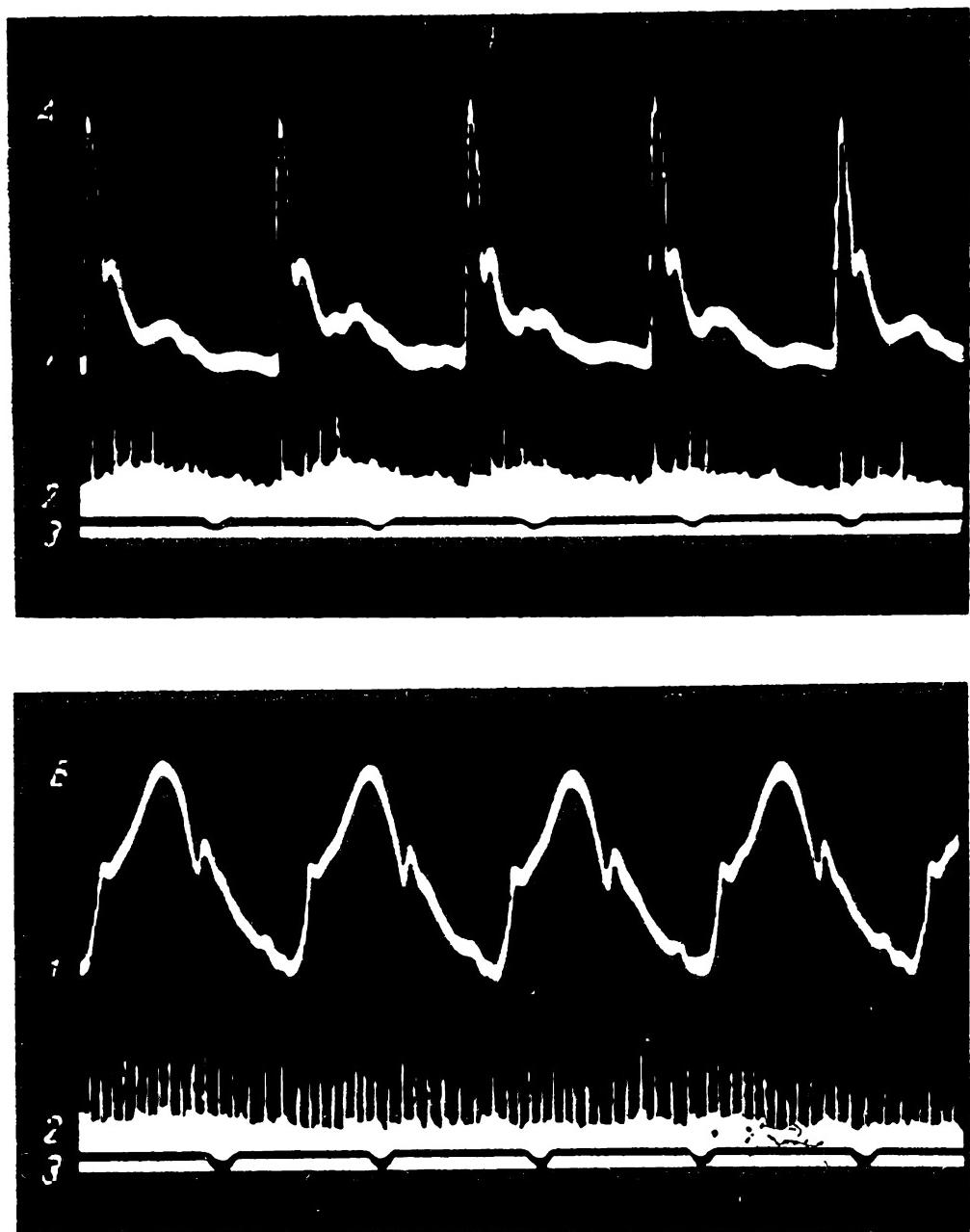
The centre of the vagus nerves of the newborn has no tone. That is demonstrated by the fact that cutting of the cardiac nerves of newborn animals, and the treatment of infants with atropine, which abolishes the effect of the vagus nerve on the heart, does not affect their heart beat.

#### REFLEX CONTROL OF CARDIAC ACTIVITY

Apart from the nerve centres in the medulla oblongata and spinal cord, a number of others, located higher, are also concerned in the regulation of cardiac activity. Stimulation of the hypothalamus in the diencephalon increases the velocity and intensity of heart contraction, while stimulation of the cerebellum and cerebral cortex (motor and premotor zones) also evokes changes in heart performance.

All the parts of the central nervous system mentioned here are involved in reflex control of cardiac activity. Reflex reactions may either inhibit, i. e. decelerate and weaken (*vagal reflexes*), or stimulate, i. e. accelerate and intensify (*sympathetic reflexes*), heart contraction.

Reflex changes in the work of the heart occur during stimulation of various receptors. Those lying in certain parts of the vascular system are of particular importance as they are stimulated by changes in blood pressure within the vessels or by humoral (chemical) stimuli. The sites where such receptors are numerous are called *vascular reflexogenic zones*. Those located at the point of division of the common carotid artery (in the carotid sinus) are particularly important as they contain the endings of the afferent nerves, whose excitation decreases the rate of cardiac contraction. These nerve endings, which are known as *pressoreceptors*, are stimulated naturally when distended by an increase in pressure. in the vessels in which they are localized. The flow of afferent nerve impulses from pressoreceptors increases the tone of the vagal centres, which makes the heart beat more slowly. The higher the blood pressure in the vascular



**FIG. 33.** Impulses recorded from a single nerve fibre passing from a receptor lying in the carotid sinus of a rabbit at mean arterial pressure of 55 (A) and 135 mm Hg (B) (after Bronk and Stella)

1 — arterial pressure registered by a membrane manometer; 2 — electrical impulse recorded from the nerve fibre; 3 — 0.2 second time-interval markers

reflexogenic zone, the higher is the rate of afferent impulses coming from the pressoreceptors (Fig. 33).

There are also reflexogenic zones influencing heart performance at the point where the right atrium joins the venae cavae. The latter have receptor nerve endings in their wall under the endothelium, which are naturally stimulated by the distension caused by an increase in blood pressure in the venae cavae. That gives rise to a reflex decrease in the tone of the vagal centres, and to stimulation of the sympathetic nervous system, as a result of which heart beats become more frequent and intense, the heart pumps more blood into the arteries from the veins, and pressure in the venae cavae

falls to normal. The phenomenon is known as the *Bainbridge reflex*.

The adjustment of cardiac performance to the requirements of a given moment is effected by the aortic and carotid reflexogenic zones through reflex inhibition of heart beat during excess cardiac activity attended with a marked increase in blood pressure in the aorta and carotid sinus, and by the reflexogenic zones of the venae cavae through reflex acceleration when the functioning of the heart is not sufficiently energetic.

Reflex changes in the performance of the heart can also be produced by stimulation of the receptors in other blood vessels. With an increase in pressure in the pulmonary artery, for example, the rate of heart beat is slowed (Parin). Cardiac activity can also be altered by stimulation of receptors in the blood vessels of many internal organs (Chernigovsky).

Receptors have also been found in the heart itself, in the endocardium, myocardium, and epicardium; their stimulation produces reflex changes in both cardiac performance and vascular

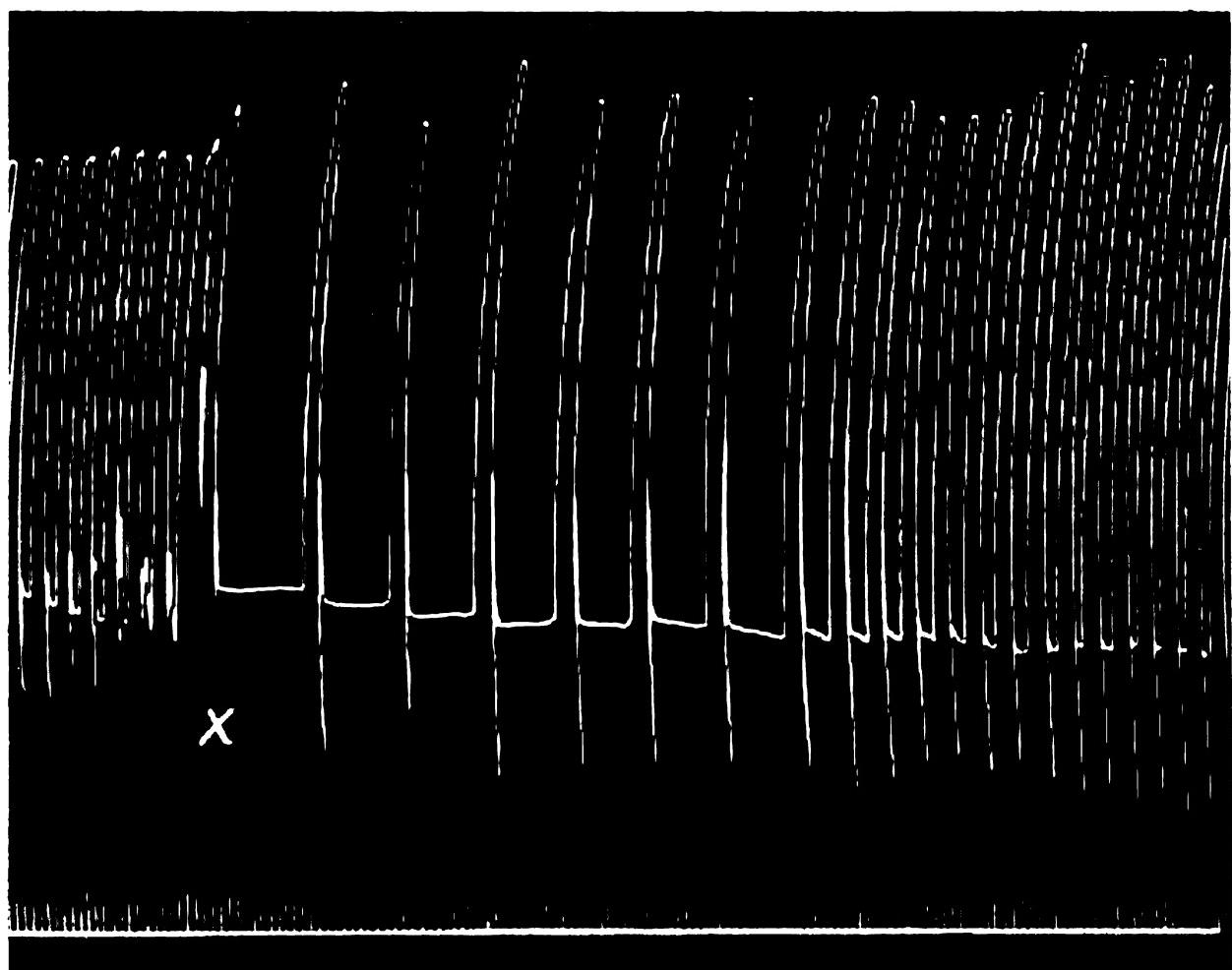


FIG. 34. Goltz's reflex in a frog. Tracings of cardiac contractions

X — shows the moment when light striking of the intestine is started. Below is the time marker

tone. Pericardial cocaineization leads to a persistent increase in blood pressure owing to arrest of the depressor impulses conducted from the epicardial receptors.

Reflex reactions occurring after an increase in pressure and distension of the atrial and ventricular walls have been described. Thus, with more blood filling the left atrium, renal urine excretion increases by 100 to 400 per cent, which leads to a reduction of blood volume and normalization of atrial filling.

A classic example of the vagal reflex was described by Goltz a century ago: a light blow on a frog's gut caused cardiac arrest of long duration (Fig. 34). Cardiac arrest resulting from a blow on the belly is also encountered in humans. The afferent pathways of this reflex extend from the intestine to the spinal cord along the splanchnic nerve and reach the nuclei of the vagus nerves in the medulla oblongata, where efferent reflex pathways begin, formed by the branches of the vagus nerve passing to the heart.

Aschner's *oculocardiac reflex* is another vagal reflex (a slowing of the heart beats to ten or twenty per minute when pressure is exerted on the eye).

Reflex acceleration and intensification of cardiac activity is encountered in response to pain stimulation, in emotional states (anger, fright, joy), and with muscular exercise, due both to impulses conducted to the heart along the sympathetic nerves and weakening of the tone of the vagal centres.

**The influence of the cerebral cortex on cardiac activity.** The fact that various emotions produce changes in heart performance indicates the importance of the cerebral cortex in its control. The changes in rhythm and force of cardiac activity often encountered in individuals just on mention or recollection of factors that produce certain emotions provide evidence of this.

Most convincing data pointing to cortical control over heart performance have been obtained by the technique of conditioned reflexes. If any stimulus, a sound stimulus, for example, is repeatedly applied together with ocular compression causing deceleration of heart beat, cardiac rhythm is slowed down later in response to the stimulus alone without compression of the eyeball (*conditioned oculocardiac reflex*). Repeated combination of any signal (sound or light) with the introduction of a drug that influences heart activity (nitroglycerin, strophanthin) gives rise to a conditioned reflex as a result of which the signal alone will cause the effect characteristic of the drug.

Conditioned reflexes underlie the phenomena which characterize the "pre-start" state of athletes. Before a competition they show changes in respiration, metabolism, and heart performance identical in character with those occurring during the events themselves. According to Krestovnikov, the rate of a skater's pulse increases by 22 to 36 beats per minute as he goes to the start of a race.

## HUMORAL CONTROL OF CARDIAC ACTIVITY

Certain substances secreted by the organs of the organism into the blood and lymph affect the heart, causing either intensification and acceleration or weakening and deceleration of its performance.

Adrenaline is most important in this respect, entering the blood from the adrenals and producing phenomena similar to those encountered with stimulation of the sympathetic nervous system, increasing the rate and amplitude of cardiac contraction.

Electrolytes also have an important role in the normal vital activity of the heart. Changes in the blood concentration of potassium and calcium salts have a most marked effect on the automaticity of the heart and on its excitation and contraction.

An excess of potassium ions inhibits all types of cardiac activity, exerting a negative chronotropic (deceleration of cardiac rhythm), inotropic (diminution of the amplitude of cardiac contractions), dromotropic (impairment of the conduction of stimulation in the heart), and bathmotropic (decrease of the excitability of cardiac muscle) effect. An excess of  $K^+$  ions brings about a diastolic arrest. Severe cardiac disorders also occur with a decrease in  $K^+$  ions content (as in hypokalaemia).

An excess of calcium ions has an opposite effect and is positively chronotropic, inotropic, dromotropic, and bathmotropic. With an excess of  $Ca^{++}$  ions the heart is arrested during a systole, while a lowered blood  $Ca^{++}$  content weakens cardiac contractions.

## THE BLOOD VESSELS

### THE MAIN PRINCIPLES OF HAEMODYNAMICS

The most important laws of *haemodynamics*, i. e. of the study of the movement of blood in the vascular system, are the same as those of hydrodynamics, i. e. the science concerned with the motion of fluids.

According to the laws of hydrodynamics, the flow of a fluid along a tube is determined by two forces: (a) by the pressure exerted upon the moving fluid, i. e. the difference between the pressure at the beginning and at the end of the tube, and (b) by the resistance encountered by the flow due to the viscosity of the fluid, its friction with the tube wall, and its turbulence. The first of these forces, the difference in the pressure, facilitates movement of the fluid, while the second, hydraulic resistance, hinders it. The ratio of the pressure difference to the resistance determines the volume flow along the tube per unit of time. The dependence is expressed by the simple equation:

$$Q = \frac{P_1 - P_2}{R}$$

where  $Q$  is the flow;  $P_1 - P_2$  is the difference between the pressure at the beginning and at the end of the tube; and  $R$  is the resistance to the flow.

This equation permits a number of calculations that are important for haemodynamics, and can be used to calculate the *total peripheral resistance* to blood flow in the systemic and pulmonary circulations.

To determine the peripheral resistance from the  $R = \frac{P_1 - P_2}{Q}$

equation, we have to know the values of the pressure at the beginning and at the end of each blood circuit, and the volume of the blood that has been expelled from the ventricles into the vascular system and returned to the atria. This amount is equal to the minute volume since, with normal physiological conditions, the heart discharges as much blood into the arteries as it has received. The values of the pressure in the aorta and in the vena cava, or in the pulmonary artery and in the pulmonary vein, can be measured directly in millimetres of mercury. When making these calculations, it must be remembered, however, that the blood is forced into the arteries not as a steady stream but as a pulsating one so that the blood pressure in the arteries at the peak of the systole differs from that at the end of the diastole. For that reason, *mean pressure values* are used (p. 137), expressing the energy of the blood if it were flowing continuously from the heart. The peripheral resistance thus determined is expressed in absolute physical values: i. e. in dynes · sec/cm<sup>5</sup>. To convert pressure expressed in millimetres of mercury into dynes, it is multiplied by the specific gravity of mercury (13.6) and by the acceleration of the force of gravity (980). The volume of blood flowing along the vessels is expressed in millilitres per second.

According to Savitsky's data the total peripheral resistance in the vessels of the systemic circulation in a human being is normally 2,500 to 1,400 dynes · sec/cm<sup>5</sup>. The resistance in the vessels of the pulmonary circulation is approximately one-tenth of that value.

The resistance to the flow of a fluid is in direct proportion to its viscosity (the viscosity of blood is five times that of water, which is taken as unity), and to the length of the tube along which it is flowing, and in inverse proportion to the radius of the tube. The relationship between these values can be expressed according to Poiseuille's law:

$$R = \frac{8 l \eta}{\pi r^4}$$

where  $\eta$  is the viscosity of the fluid;  $l$  is the length of the tube; and  $r$  is the radius of the tube.

The equation was deduced from studies of the motion of a fluid in hard tubes and cannot be used for a precise estimate of the resis-

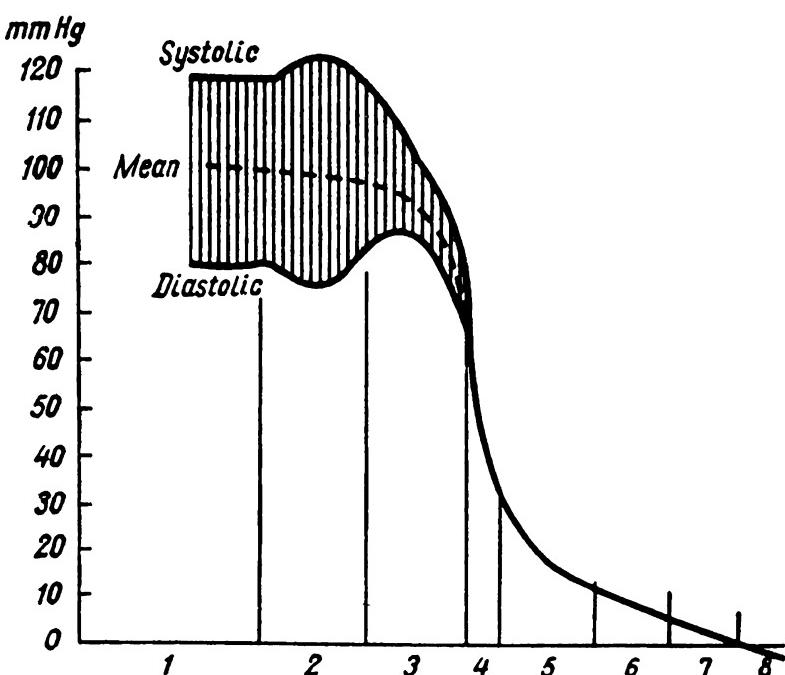
tance encountered by the blood flow in the blood vessels. It does not take into account all the natural conditions occurring in haemodynamics: i. e. the elasticity of the vascular wall, the changes in vascular diameter with changes in the pressure of the blood, turbulence, etc. The equation nevertheless reflects the dependence of the resistance on the width and length of the vessels and on the viscosity of the blood. It shows that maximum resistance to blood flow is encountered in the narrowest blood vessels, the arterioles and capillaries (owing to the shortness of the capillaries the resistance in them is much less than in the longer arterioles).

The resistance encountered in the various vessels can be judged from the difference between the pressure at their beginning and at their end; the greater the resistance to blood flow, the more force is expended to push it along the vessel, and the greater is the fall in pressure along it. A diagram of blood pressure measurements in various vessels shows that pressure drops by only 10 per cent along the large and medium-sized arteries, and by 85 per cent in the arterioles and capillaries. That means that 10 per cent of the energy utilized by the ventricles to expell blood is spent on its propagation along the large and medium-sized arteries, and 85 per cent on its propagation in the arterioles and capillaries. The distribution of pressure according to the different parts of the arterial system is shown in Fig. 35.

With a known volume flow (expressed in millilitres per second), the linear velocity can be calculated in millimetres per second. The linear velocity ( $V$ ) shows the velocity of the motion of blood particles along the vessel and is equal to the volume flow ( $Q$ ) divided by the cross-sectional area of the blood vessel:  $V = \frac{Q}{\pi r^2}$ .

The linear velocity calculated from this formula is the mean velocity. In reality, the linear velocity of blood particles moving in the centre of the flow (along the longitudinal axis of the vessel) differs from that of particles moving near the vessel wall, being maximum for the former and minimum for the latter, since friction between the particles and the vascular wall is particularly great.

It has already been mentioned that the volume of blood flowing through the aorta and venae cavae or through the pulmonary artery or pulmonary veins is the same. The amount of blood ejected from the heart corresponds to that received by it. Consequently, the volume of blood flowing per minute through the entire arterial system, or through the arterioles, through all the capillaries, or through the venous system is equal in both the systemic and pulmonary circulations. With the same volume of the blood passing through vessels with different cross-section, however, the linear velocity of blood flow differs, depending on the total breadth of the vascular bed. This is precisely what follows from the equation expressing



**FIG. 35. Changes in the systolic, diastolic, and mean pressure in different parts of the vascular system**

1 — aorta; 2 — large arteries; 3 — small arteries; 4 — arterioles; 5 — capillaries; 6 — venules; 7 — veins; 8 — venae cavae

the relation between the linear velocity and volume flow; the larger the total cross-sectional area of the vessels, the lower is the linear velocity of blood flow. The narrowest point in the cardiovascular system is the aorta. The total area of the vascular bed increases with the ramification of the arteries, in spite of the fact that each new branch is narrower than that from which it originates, because the sum total of the arterial lumina is larger than the lumen of the initial artery. The capillary network constitutes the most extensive vascular bed because the total of all the capillary lumina is between 600 and 800 times the size of the aortic lumen; owing to that blood flows much more quickly along the aorta than in the capillaries.

The linear velocity of blood flow in the veins again increases compared to that in the capillaries because the blood channel becomes narrower as one vein joins another. In the venae cavae it becomes half that in the aorta. The distribution of blood flow velocities within the vascular system is shown in Fig. 36.

Since blood does not flow from the heart in a continuous stream but is ejected in several portions, blood flow is pulsating. Clearly the linear velocity and volume flow are constantly changing owing to that, becoming maximum in the aorta and pulmonary artery during a systole and falling during a diastole. In the capillaries and veins blood flow is continuous at all times and, consequently, linear velocity is also constant. In the transformation of the pulsating flow into a continuous one, the properties of the arterial walls are significant.

Arteries are divided into two groups according to the structure of their walls. The large arteries constitute a group of vessels of an *elastic type*, while those of the medium and small calibre are vessels of a *muscle type*. Extremely elastic properties of the aorta and large

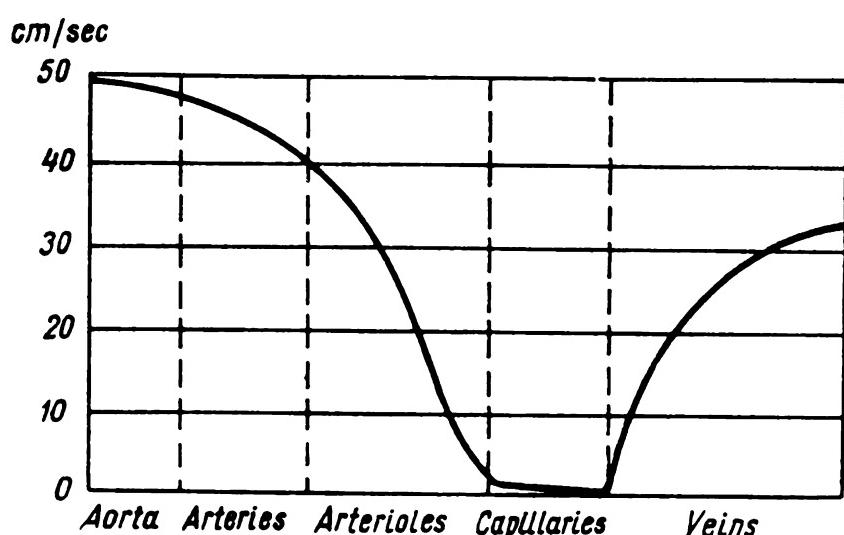


FIG. 36. Changes in the linear velocity of the blood flow in different parts of the vascular system

arteries are responsible for the continuous flow of blood through the entire vascular system.

The importance of elasticity of the vascular wall in balancing the flow of fluid is demonstrated by the following experiment: water is allowed to flow from a container in an interrupted stream simultaneously through two tubes one rubber and the other glass, both terminating in fine capillaries. The water will flow from the glass tube in spurts, but continuously and in larger amount from the rubber one. An elastic tube is able to smooth out and increase the flow of fluid because the distension of its walls by a portion of the fluid gives rise to elastic tension in it, i. e. some of the kinetic energy of the fluid is transformed into the potential energy of elastic tension. Part of the kinetic energy produced in the heart during a systole is expended on distension of the aorta and the large arteries originating from it, which together form an elastic or *compression chamber* that receives an abundant amount of blood, and is distended by it; during this process the kinetic energy produced in the heart is transformed into elastic tension of the arterial walls. When the systole ends, that tension maintains blood flow during the diastole.

#### ARTERIAL PRESSURE

The pressure of the blood within the arteries of animals, and occasionally of humans, is measured by inserting into an artery a glass cannula or a needle connected to a manometer by a tube with rigid walls. The cannula and connecting tube are filled with an anti-coagulant to prevent the coagulation of blood in them.

The blood pressure used to be measured by means of a mercury manometer supplied with a float that traced pressure oscillations on the drum of a kymograph. The apparatus, however, had considerable inertness and produced a distorted record. For that reason, electro-manometers are used now, whose inductivity or active resistance

alters with changes in the pressure. They are highly sensitive and non-inert.

Other methods, namely indirect, are used to measure blood pressure in humans, besides this direct method of introducing a cannula or needle into an artery. They are based on measuring the pressure that has to be exerted on the wall of a vessel in order to stop the flow of blood in it. A hollow rubber cuff, connected with a rubber bulb for pumping air into it and with a mercury manometer (Riva-Rocci sphygmomanometer) is applied to the arm of the examined person. On being inflated with air, the cuff compresses the arm like a ring, while the manometer shows the level of the pressure exerted. The technique also employs auscultation of the sounds arising in the artery peripherally of the applied cuff, as suggested by Korotkov.

No sounds are usually heard above an uncompressed artery when blood is flowing in it. If the pressure in the cuff is raised above the level of the systolic pressure in the artery, it will completely compress the artery and flow of blood will be arrested. No sounds will then be heard either. But if air is now released gradually from the cuff (i. e. decompression is produced), then as soon as its pressure falls slightly below that of the artery blood flow will overcome the resistance in the compressed area during a systole and will rush through the partly decompressed segment of the artery under the cuff. Moving with great kinetic energy, it will strike the arterial wall and will produce an audible sound distally to the cuff. The pressure within the cuff at which the first sounds appear in the artery corresponds to the *maximum* or *systolic pressure*. Further reduction of pressure in the cuff brings it to the point where it drops below the level of the diastolic pressure and blood begins to flow in the artery during both the systole and the diastole. Sounds in the artery distally of the cuff disappear at that moment. The pressure in the cuff at that moment is taken as the *minimum* or *diastolic pressure*.

Comparison of arterial pressures determined in this way by *Korotkov's method* with those recorded from the same person on an electromanometer as described above has shown them to be close, but not always identical.

Pressure in the arteries is determined: 1) by the volume of the blood ( $Q$ ) entering them as a result of cardiac activity; and 2) by the resistance to the blood outflow into the small arteries, arterioles, and capillaries ( $R$ ). The relationship is expressed by the simple formula:  $P = Q \cdot R$ .

In accordance with this formula, an increase of minute volume, or cardiac output (with transfusion of large amounts of blood), leads to an increase in blood pressure. A decrease of the minute volume (as a result of bleeding, for example) causes a fall in arterial pressure.

A fall in arterial pressure due to a decrease in venous return of blood to the heart and, consequently, a decrease in the minute

volume of blood ejected by the heart, also occurs with dilatation of the capillary and venous bed. In that case, blood accumulates there, and the minute volume, and consequently the arterial pressure, decrease in the same way as with a reduction in the mass of circulating blood following bleeding.

The relationship between blood pressure and the ejection of blood by the heart can be illustrated by the effect caused by stimulation of the vagus nerve (see p. 122). With weak stimulation deceleration and weakening of the heart beat results in a decrease in the flow of blood to the arteries, so that blood pressure decreases. With strong vagal stimulation resulting in cardiac arrest and cessation of blood flow to the arteries, blood pressure drops almost to zero. It can be seen from the formula given above that peripheral resistance to blood flow is also a factor determining the level of arterial pressure. That pressure is maximum in the arterioles; when their lumina are narrowed and resistance to the flow is increased, arterial pressure rises; and conversely, dilatation of the arterioles leads to a decrease in pressure in the arteries.

Peripheral resistance, and consequently the level of the arterial pressure, are influenced by the viscosity of the blood: the higher the viscosity, the greater is the resistance in the arterioles, and the higher the pressure in the arteries.

Intra-arterial pressure is not constant; but it exhibits continuous fluctuations, rising above and dropping below a certain mean level, which produce three types of wave on the blood pressure curve.

*Waves of the first type* are the most frequent and arise from the contraction of the heart. A certain amount of blood enters the arteries with each systole and increases their elastic distension. The inflow of blood to the aorta and pulmonary artery during a ventricular systole exceeds the outflow, so that the pressure within them increases. During a diastole ejection of blood from the ventricles into the arterial system ceases and only the outflow of blood from the large arteries continues; their walls become less distended and pressure falls. Pressure fluctuations spread from the aorta and pulmonary artery to all their branches, gradually waning. The rise in arterial pressure as a result of the systole is the *maximum or systolic pressure*, while the fall during the diastole is the *minimum or diastolic pressure*. The difference between the two, i. e. the amplitude of pressure fluctuation, is known as the *pulse pressure*. Other conditions being equal, pulse pressure is in direct proportion to the amount of blood pumped by the heart during each systole, and to a certain extent is a characteristic of the systolic volume.

Pulse pressure is highest in the arteries lying near to the heart. The further from the heart, the lower it is, i. e. the difference between the systolic and diastolic pressures gradually becomes obliterated.

Pulse pressure waves do not occur in the arterioles and capillaries; the pressure in them is constant and does not change with a systole or diastole.

As well as systolic, diastolic, and pulse pressures, a mean pressure is determined. *Mean pressure* is the average between the systolic and diastolic pressure values, and would, in the absence of pulse fluctuations, be capable of producing the same haemodynamic effect as that observed with the natural, fluctuating blood pressure. Mean pressure is the force of continuous blood flow.

The value of the mean pressure can be determined using a mercury manometer supplied with a tap between its two limbs. Partial closing of the tap interferes with the rapid oscillations of the mercury caused by the systolic rise and diastolic drop in pressure. The pressure curve will then be traced as an almost straight line not reflecting pulse oscillations. The difference in levels of the two limbs of the manometer corresponds to the mean pressure.

Since the diastolic fall in pressure lasts longer than the systolic rise, the value of the mean pressure is closer to that of the diastolic than to that of the systolic, and in any one artery it is more constant than either, as they are extremely variable.

Apart from pulse oscillations, the blood pressure curve shows *waves of the second type*, which correspond to respiratory movements; because of that they are known as *respiratory waves*. Inspiration is accompanied with a decrease in blood pressure, and expiration by an increase.

*Waves of the third type* are also sometimes encountered as much slower rises and falls in pressure, each embracing a number of respiratory waves. They are caused by a periodic increase and decrease in the tone of the vasomotor centre (p. 148), and are most frequently associated with oxygen deficiency in the brain, with low atmospheric pressure, for example, or following blood loss, or with intoxication by certain poisons, etc.

The systolic pressure in a middle-aged adult, measured directly, is 110 to 125 millimetres of mercury in the aorta, and 105 to 120 millimetres in the main arteries of the limbs. Those values show that the drop in arterial pressure in the main arteries is not very marked. The sharpest fall occurs in the small arteries, particularly in the arterioles, and reaches 25 to 30 millimetres of mercury at the arterial end of a capillary.

In clinical practice arterial pressure is usually measured in the *brachial artery*; in healthy persons between 15 and 50 years of age the *systolic pressure* measured there by Korotkov's method varies from 105 to 120 millimetres of mercury. In those over fifty it increases as a rule, and at the age of sixty averages 135 to 140 millimetres. Systolic pressure in the newborn is 40 millimetres, but rises to 70 in a few days and reaches 80 millimetres of mercury by the end of the first month.

The *diastolic pressure* in the brachial artery of healthy middle-aged individuals varies between 60 and 80 millimetres on the average, pulse pressure or the pulse difference being 35 to 50 millimetres of mercury.

A number of factors influence the level of blood pressure. Emotional excitement, anger, or fright, for example, cause a marked increase, mainly in the systolic pressure, owing to intensification of cardiac performance and narrowing of the vascular bed. These changes are due to reflexes and partly to adrenaline secreted into the blood.

Physical effort is attended with a drastic increase in blood pressure mainly owing to intensification of heart activity. Systolic pressure may go as high as 180 or 200 millimetres of mercury. Diastolic pressure also increases in most cases (up to 100 or 110 millimetres); and pulse pressure rises, indicating an increase in the systolic volume.

Individuals suffering from cardiovascular insufficiency show a slight increase in systolic pressure and a marked increase in diastolic pressure during intense muscular effort; pulse pressure decreases.

#### ARTERIAL PULSE

The rhythmical expansion of the arterial wall caused by the systolic rise in pressure is called the *arterial pulse*. Arterial pulsation can easily be felt on any artery accessible to palpation, as the radial and temporal arteries, the dorsal artery of the foot, etc.

A pulse wave, or wave of increased pressure, arises in the aorta at the moment blood is ejected from the ventricle, when the pressure in the aorta rises sharply and its wall distends. The wave of increased pressure, and expansion of the arterial wall caused by it, spread from the aorta to the arterioles and capillaries at a definite rate, dying out in the capillaries.

The rate at which the *pulse wave spreads* is not governed by the velocity of blood flow. The *maximum linear velocity of arterial blood flow* does not exceed 0.3 to 0.5 metre per second, while the pulse wave spreads at a rate of 5.5 to 8.0 metres per second in the aorta, and 6.0 to 9.5 metres per second in the peripheral arteries in young and middle-aged individuals with normal elasticity of the vessels and normal blood pressure. The pulse wave velocity increases with age, particularly in the aorta, as the vessels lose their elasticity.

For detailed analysis of separate pulse waves, recordings are made on moving paper or film by special instruments, or *sphygmographs*, of which there are several types. One registers oscillations of the pulse wave by means of a system of small levers, another is based on a pneumatic technique using a cuff fixed on the arm or leg, while a third employs an optical method. At present pick-ups are used,

which transform the mechanical fluctuations of the arterial wall into electrical phenomena, which are registered.

Two main parts are distinguished on the pulse curve (*sphygmogram*) of the aorta or large artery: a) an *anacrotic* on a rising part of the curve, and b) a *catacrotic* on the descending part of the curve.

The anacrotic rise results from the increase in arterial pressure and ensuing distension of the arterial walls at the beginning of the ejection phase. The catacrotic descent of the curve occurs at the end of the systole, as pressure in the ventricle begins to fall. At the start of ventricular relaxation, when the pressure in the ventricular chamber is lower than in the aorta, blood discharged into the arterial system rushes back toward the ventricle; pressure in the arteries falls sharply and a deep notch, or *incisure*, appears on pulse curves recorded from the main arteries. Return of blood to the heart, however, is checked by the semilunar valves, which are pushed shut by the backward flow. The return stream of blood rebounds against the valves and gives rise to a secondary wave of increased pressure which again distends the arterial walls. As a result, a secondary or *dicrotic* rise appears on the sphygmogram.

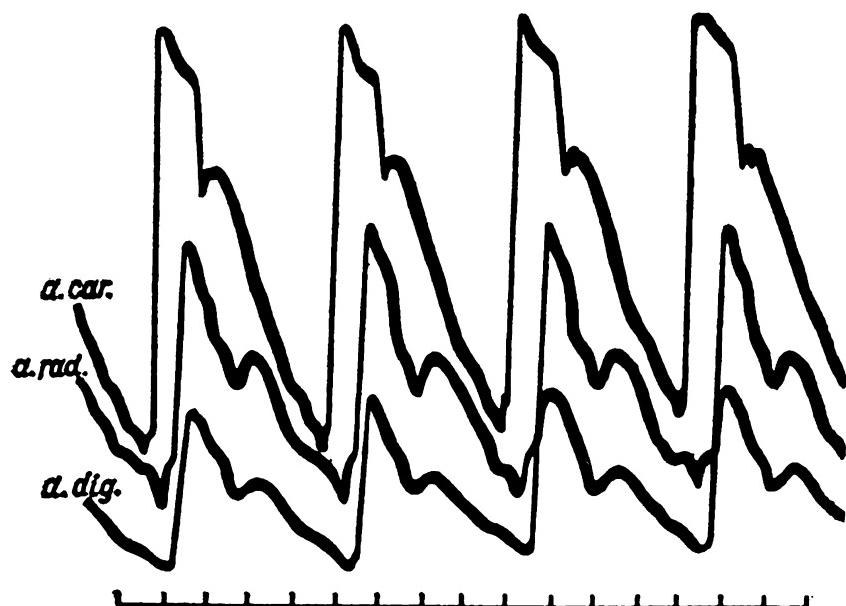
The curve recorded from the aorta or main vessels branching directly from it (the *central pulse*) differs somewhat from the pulse curve of the peripheral arteries (Fig. 37).

Examination of the pulse reveals a number of its properties: its rate, velocity, amplitude, tone, and rhythm. *Pulse rate or frequency* per minute characterizes the rate of cardiac contraction. The *velocity of the pulse* is determined by the speed with which pressure rises in the arteries at the moment of the anacrotic ascend and declines during the catacrotic descend. *Pulsus celer* (a quick pulse) and *pulsus tardus* (an abnormally slow pulse) are distinguished; the former is encountered in insufficiency of the aortic valve, when the ventricle ejects an increased amount of blood and some returns quickly to the heart through the defect in the valve. *Pulsus tardus* occurs with stenosis of the aortic orifice, when the blood is pushed into the aorta more slowly than normal.

The *amplitude of the pulse* characterizes the expansion of the arterial wall during the pulse thrust.

The hardness of the pulse is determined by the amount of pressure required to compress the artery so that the pulse disappears.

Synchronous registration of an electrocardiogram and a sphygmogram on the same tape yields important findings that are of practical help in judging cardiac activity in certain heart conditions. "*Pulse deficit*" is sometimes encountered, when an occasional wave of ventricular excitation is not attended with discharge of blood into the vascular system and by a pulse thrust. Some systoles are so weak, owing to a small systolic discharge, that they do not give



**FIG. 37.** Sphygmograms recorded synchronously from the carotid, radial, and digital arteries

rise to a pulse wave which reaches the peripheral arteries; pulse rhythm then becomes irregular (*allorhythmic pulse*).

#### ARTERIAL BLOOD FLOW

It has already been pointed out that volume flow and linear velocity are distinguished in the blood flow. They vary in different organs of the body according to the development of their vascular network and to the work performed.

The blood vessels dilate in a working organ and their resistance therefore diminishes. Since this local vascular dilatation has little effect on the general pressure of the blood, its volume flow in these vessels increases.

#### Blood flow in various organs (in millilitres per 100 grammes of organ weight per minute)

Organ	Blood flow	Organ	Blood flow
Thyroid	560	Brain	65
Kidneys	420	Spleen	70
Liver	150	Stomach	35
Heart (coronary blood flow)	85	Muscles of the arms and legs (at rest)	2-3
Intestine	50		

Several methods have been suggested for measuring the volume flow and linear velocity, but all are rather complicated and are of little use for studying this important haemodynamic index in human beings. All involve exposure of the arteries and the application of different devices to them. One of the most precise methods cur-

rently used, the ultra-sonic, consists, for example, in placing two small piezoelectric plates on the artery at a small distance one from the other, which transform mechanical oscillations into electrical ones and, vice versa, electrical oscillations into mechanical ones. High-frequency voltage is fed to the first plate and is transformed into ultra-sonic oscillations that spread with the blood to the second plate and are received by it and re-transformed into high-frequency electrical oscillations. Having determined how soon the ultra-sonic oscillations reach the second plate, and how soon oscillations from the second plate spread to the first against the direction of the blood flow, one can calculate the velocity of the flow. The faster the flow, the quicker the ultra-sonic oscillations spread with it and the slower against it.

The mean linear velocity of aortic blood flow in dogs and monkeys is about 30 to 40 centimetres per second. It reaches one metre per second during rapid ejection of blood from the heart and drops almost to zero centimetres per second at the end of a diastole. Its value in humans can be calculated if the minute volume of blood discharged from the heart and the diameter of the aorta are known (see the equation on p. 132).

#### CAPILLARY CIRCULATION

The importance of the capillaries in vital processes is the interchange of substances between the blood and tissues that occurs across their walls. Capillary walls are composed of a single layer of endothelial cells through which substances dissolved in the blood diffuse. The total number of capillaries in the systemic circulation is thousands of million, and because of that blood flow in them is extremely expansive.

The sum of the cross-sections of all functioning capillaries is approximately 600 to 800 times the aortic cross-section. That is evident from the fact that the linear velocity of blood in them, 0.3 to 0.5 millimetre per second, is about 600 or 800 times as small as that in the aorta. It can be measured by direct microscopy of the movement of erythrocytes in a capillary.

Each separate capillary is 0.3 to 0.7 millimetre long and about 8.0 microns in diameter.

It has been calculated that one millilitre of blood in the capillaries of a muscle has a surface of 0.5 of a square metre in contact with the thin capillary endothelium. This large contact surface facilitates interchange of substances between the blood and the tissues there, particularly interchange of gases.

The shape and size of the capillaries and their number vary with the organs. The number of capillaries per square millimetre in a cross-section of tissues with intense metabolism is greater than in those in which it is less intense. In the heart, for example, the

number of capillaries per square millimetre of cross-section is double that in skeletal muscle.

Two types of capillaries are distinguished: a) those that form the shortest passages between the arterioles and venules (known as main capillaries); and b) those that form the lateral branches of main capillaries. Branches arising from the arterial end of one capillary and emptying into the venous end of another form the capillary network. According to Mchedlishvili, the volume flow and linear velocity of blood in the main capillaries exceed those in lateral branchings.

The pressure of the blood in capillaries has been measured directly; under visual control through a binocular lens an extremely fine cannula was introduced into a capillary, counter to the blood flow, and connected to a burette filled with physiological solution. The pressure in the burette could be altered at will and measured; it was equal to the pressure within the capillaries when the erythrocytes that penetrated into the cannula remained still, moving neither back toward the capillary nor forward in the cannula.

The pressure in capillaries lying on a level with the heart is approximately 25 to 30 millimetres of mercury at the arterial end, and eight to twelve millimetres at the venous end.

Krogh and co-workers determined the total number of capillaries per square millimetre of cross-section of skeletal muscle, employing intravital staining with India ink. Dog muscle was found to have about 2,500 capillaries per square millimetre of cross-section. Through special experiments, Krogh established the rate of oxygen diffusion in the tissues, and concluded from his findings that, if blood were always flowing through all the capillaries of the muscle, the oxygen tension in the tissue should then be the same as that in the blood in the capillaries. It was found, however, that the oxygen tension in muscle at rest was very low (near to zero), from which it is evident that blood flows along only a small number of capillaries in a resting muscle, which, being open, are as it were "on duty", while the remaining capillaries are constricted and do not let blood through. That that actually occurs was shown by Krogh's count of the capillaries in a working muscle of one limb and in a resting muscle of the other limb of the same animal. The table below gives the data obtained from examination of the capillaries in the muscle of a guinea pig.

	Number of capillaries per mm <sup>2</sup> of cross-section
At rest	31 to 270
During work	2,500
Total number of capillaries	3,000

During rest, the "duty" capillaries are regularly relieved by others. The factor responsible for some capillaries being open and others closed is not known yet. There are evidently no reserve capillaries, and any one may be "on duty" at a given moment.

Krogh established that the tone of closed capillaries is extremely high. They cannot be filled with blood *intra vitam* even with high arterial pressure, but atonic capillaries easily become filled even with low pressure.

Since the capillary wall consists only of endothelium and is devoid of muscle elements, the question of how they close naturally arises. It was assumed that it occurred through contraction of the Rouget cells, peculiar dactylate cells that are occasionally found embracing the capillaries. That assumption has been refuted. The level of pressure in the arterioles has a significant effect on changes in the capillary lumen; as it rises the number of functioning capillaries increases. Thus the arterioles serve as "taps" that regulate the filling of the capillaries.

**Arterio-venous anastomoses.** Direct communication between arterioles and veins are encountered in certain parts of the body, for example, in the skin, lungs, and kidneys. They are known as arterio-venous anastomoses and are the shortest passages between the arterioles and veins. They are usually closed and the blood flows along the capillary network, but when they open some blood can enter the veins, by-passing the capillaries.

In this way arterio-venous anastomoses fulfil the function of shunts regulating capillary circulation. Changes in capillary blood flow in the skin with a rise or fall in external temperature is an example. With the external temperature rises (above 35°C), or falls (below 15°C), anastomoses located in the skin open, and blood from the arterioles flows directly into the veins, which protects it from overheating or over-cooling, since not all the blood flows along the capillary network of the skin where it either absorbs heat or loses it.

#### CIRCULATION IN THE VEINS

Blood flow in the veins is an important factor of circulation since it determines the diastolic filling of the heart. It has a number of peculiarities.

Owing to the thinness of their muscle coat, veins are more elastic than arteries and their walls therefore become markedly distended even at small pressures, and large amounts of blood may accumulate in them.

**Venous pressure.** The venous pressure of humans can be measured by introducing a hollow needle into a superficial vein (usually the cubital one), and connecting the needle to a manometer. Pressure in the veins on the outside of the chest varies between five and nine millimetres of mercury (between 65 and 120 millimetres of water).

In determining the value of venous pressure it is necessary that the vein used be on a level with the heart; pressure in the veins of the legs, for example, when a person is standing, includes the weight of the column of blood filling them. For that reason, pressure in the veins of the legs is measured with the patient lying down, so as to eliminate the hydrostatic component.

The pressure in veins lying around the chest does not differ much from atmospheric pressure but varies with the phase of respiration. During inspiration, when the chest expands, the pressure in the veins drops and becomes negative, i. e. less than atmospheric pressure; during expiration it increases (not more than two to five millimetres of mercury during a normal expiration). With forced expiration, in particular with straining, when the chest becomes compressed and the pressure within it rises sharply, pressure in the venae cavae also increases and prevents outflow of blood from the veins of the abdomen and limbs; the venous return of blood to the heart diminishes, and as a result arterial pressure drops, which explains the occasional occurrence of syncope when people are straining heavily.

Since pressure in the veins lying near the chest becomes negative during inspiration (for example, in the jugular vein), injury to them is dangerous; atmospheric air can enter them and cause air embolism, i. e. occlusion of the arterioles and capillaries with bubbles of air.

The linear velocity of blood flow is less in the veins than in the arteries, because the venous vascular bed is two or three times wider than the arterial, which results in a slower flow of blood in accordance with the laws of haemodynamics. The linear velocity in peripheral veins of medium calibre varies between six and fourteen centimetres per second; in the venae cavae it reaches 20 centimetres per second.

Blood flows along the veins of the systemic circulation not only because of the force exerted by contraction of the left ventricle much of which has already been spent in the movement of the blood along the arterioles and capillaries where resistance is very high; additional factors are also of importance here. One is the fact that the endothelium of the veins (with the exception of the venae cavae, the veins of the portal system, and the small venules) forms folds which act as real valves allowing the blood to flow only in the direction of the heart. For that reason, any force that compresses the veins and causes blood to move, facilitates venous blood flow, the valves preventing it from backing up.

Two principal additional forces contribute to the movement of blood along the veins: 1) the aspiration effected by the chest, and 2) the contraction of the skeletal muscles. The respiratory action of the chest has already been discussed; it particularly facilitates blood flow in the veins during inspiration. The work of the skeletal muscles contributes to venous circulation because both the veins in the muscle itself and those adjoining it become compressed during its contraction. As the pressure in the veins is very low, blood is squeezed out of

them in the direction of the heart when they are compressed (the valves preventing a backward flow). Hence rhythmical movements (sawing wood or walking, for example) act like a pump and greatly increase the rate of venous circulation. On the other hand, static work, i. e. prolonged contraction of the muscles, which leads to protracted compression of the veins, hinders venous circulation.

**Venous pulse.** There are no fluctuations of pulse pressure in the small and medium-sized veins, but they are encountered in the main veins located close to the heart, and are known as venous pulse. Venous pulse differs in origin from arterial pulse, and occurs owing to blocking of blood flow to the heart during the atrial and ventricular systoles. With each contraction of those parts of the heart the pressure in the veins increases and pulsations of the venous wall occur. It is easiest to record the pulse from the jugular vein.

Three waves, *a*, *c*, and *v*, are distinguished on the trace of a venous pulse, or *phlebogram* (Fig. 38). The *a* wave corresponds to the systole of the right atrium and is produced when the cavae orifices of the venae in the atrium close by contraction of the ring-like band of muscle fibres and flow of blood into the atrium is temporally stopped. Thus, a short-term stasis occurs in the veins and leads to distension of their walls. During the diastole of the atrium blood again enters it easily, which is seen as a sharp, downward deflection on the phlebogram. It is soon followed by a small *c* wave due to the thrust produced by the pulsating carotid artery lying close to the jugular vein. Then a new downward deflection appears which is again followed by a new rise, the *v* wave, which results from the atrium being filled with blood at the end of the ventricular systole to such an extent that no more blood can enter them, so that blood accumulates in the veins and distends their walls

#### TOTAL CIRCULATION TIME

The time required for the blood to flow along both the systemic and pulmonary circulation is known as the total circulation time.

It can be measured by several methods that involve intravenous injection of a substance not commonly encountered in the body and determination of the interval required for the substance to appear in the corresponding contralateral vein or to produce the effect characteristic of it. A solution of the alkaloid lobeline which acts upon the respiratory centre located in the medulla oblongata is injected, for example, into the cubital vein, and the interval between its introduction and the appearance of a momentary respiratory arrest or a cough is determined. That occurs when lobeline molecules, having circulated through the cardiovascular system, affect the respiratory centre and cause a change in respiration or a cough.

More recently the total circulation time for both circuits (or for the systemic and the pulmonary circulations separately) has been

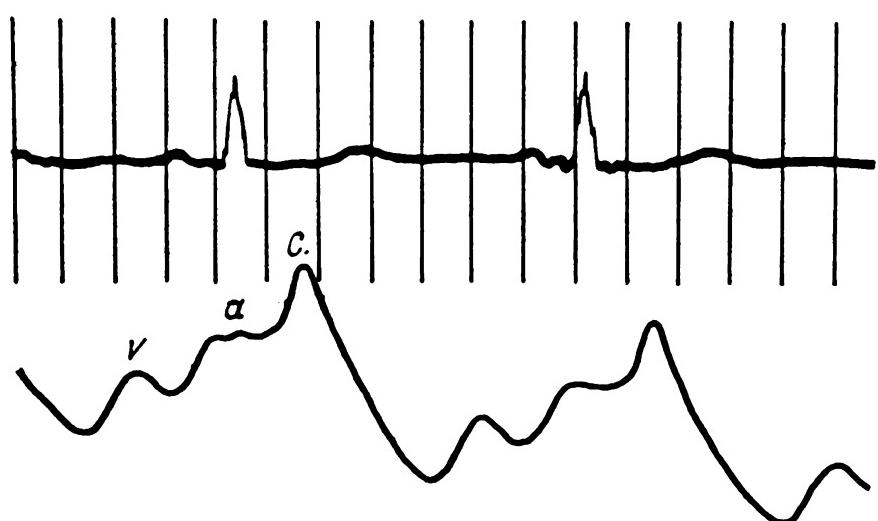


FIG. 38. Synchronous recording of a venous pulse and electrocardiogram (discussed in the text)

determined by means of radioisotope of sodium and an electron counter. Counters are applied to different parts of the body close to the main vessels and in the region of the heart. After the isotope has been introduced into the cubital vein, the time of the appearance of radioactive radiation in the region of the heart and of the vessels is determined.

The circulation time in humans is 27 heart systoles on average. With 70 to 80 cardiac contractions per minute it takes between 20 and 23 seconds for the blood to traverse the complete circuit of the cardiovascular system. It should be remembered, however, that the rate of the flow along the axis of the blood vessel is higher than along its walls, and that the extension of all the vascular regions is not the same. For that reason, not all the blood completes the circuit within this time, and the interval mentioned is the shortest.

Research on dogs has shown that pulmonary circulation accounts for one-fifth of the circulation time and systemic circulation for four-fifths.

#### CONTROL OF VASCULAR CIRCULATION

There is a complex system of control mechanisms ensuring a definite, dynamically variable co-ordination between cardiac performance, the size of the lumen and the capacity of the vascular bed, and the amount of circulating blood, which guarantees optimal conditions for the circulation in the organs and tissues in accordance with their functional condition, whether they are at rest or working.

#### VASCULAR INNERVATION

The blood vessels are supplied with nerves that regulate the calibre of their lumen and are responsible for their constriction or dilatation.

The *vasoconstrictors*, or nerves that cause constriction of the vessels, form part of the sympathetic nervous system. Their existence was first revealed by Walter in 1842 in experiments on frogs and later by Claude Bernard (1852) in experiments on the ear of a rabbit. Stimulation of the sympathetic nerve on the rabbit's neck causes the corresponding ear to become pale, owing to constriction of its arteries and arterioles, and the temperature and bulk of the ear to diminish. The principal vasoconstrictors in the abdominal organs are the sympathetic fibres included in *n. splanchnicus*. In the limbs the sympathetic vasoconstrictor fibres come, firstly, from the mixed spinal nerves (stimulation of which usually results in constriction of the vessels of the limb) and secondly, along the arterial walls (in the adventitia).

Cutting of the sympathetic vasoconstrictors leads to dilatation of vessels in the region innervated by them. Evidence of that was produced by Claude Bernard's experiment involving cutting of the sympathetic nerve on one side of the neck with resultant dilatation of vessels, showing in the ear on the side operated on becoming red and warm. Similarly, cutting of *n. splanchnicus* is followed by a sharp increase of blood flow in the abdominal organs thus deprived of vasoconstrictive sympathetic innervation. The experiments described show that the blood vessels are under the continuous constrictive influence of sympathetic nerves which maintain the constriction of the arterial muscular wall at a constant level (*arterial tone*).

Stimulation of the peripheral end of a dissected sympathetic nerve can restore the normal level of the arterial tone, a rate of one or two impulses per second being sufficient to produce the effect (Folkov, Khayutin). Changes in the rate of the impulses reaching the arteries may cause constriction (with acceleration of the rate) or dilatation (with deceleration).

The *vasodilative effect* was first revealed during stimulation of certain nerve branches belonging to the parasympathetic system. Stimulation of the chorda tympani, for example, caused dilatation of the vessels in the submandibular gland, stimulation of the *n. lingualis* resulted in dilatation of the vessels of the tongue, while stimulation of *n. pelvis* led to dilatation of the vessels of the genitalia.

In some organs, e. g. the skeletal muscles, dilatation of arteries and arterioles can be caused by stimulation of sympathetic nerves that contain vasodilators as well as vasoconstrictors. As a rule, however, it leads to constriction of the vessels, dilatation occurring only in particular cases, for example, following the introduction of ergotoxine which causes paralysis of the sympathetic vasoconstrictors.

Dilatation (mainly of the blood vessels of the skin) can also result from stimulation of the peripheral ends of the posterior spinal

roots which include the afferent (sensory) fibres. Vascular dilatation will occur in the areas of the skin supplied with sensory nerve fibres from the stimulated root.

The mechanism of the effect exerted by the vasodilator nerves is still not quite clear. It has been established more recently that it is due to vasodilator substances produced through their stimulation. Thus, acetylcholine, which causes dilatation of the arterioles, is produced in the endings of the sympathetic vasodilators of skeletal muscle on their stimulation. On stimulation of the posterior spinal roots, vasodilator substances are apparently produced at some site close to the vessel, but not in its wall.

#### VASOMOTOR CENTRES

Constriction or dilatation of the vessels occurs under the influence of impulses from the central nervous system. Ovsyannikov established in 1871 that the nerve centre responsible for maintenance of a definite calibre of the arterial bed, the *vasomotor centre*, is situated in the medulla oblongata. Its location was traced by making sections at various levels of the brain stem. Cutting above the mid-brain in a dog or a cat caused no change in blood pressure, but a section made between the medulla oblongata and the spinal cord leads to a fall of systolic pressure in the carotid artery from the normal 100-120 to 60-70 millimetres of mercury.

Hence it follows that the vasoconstrictor centre is located in the medulla oblongata and that it is marked by tone, i. e. is in a state of persistent constant excitation. If its influence is abolished, the vessels become dilated and arterial pressure falls.

More detailed analysis has shown that the vasomotor centre of the medulla lies in the floor of the fourth ventricle and consists of two parts, the *pressor* and the *depressor*. Stimulation of the former causes constriction of the arteries and a rise in blood pressure, while stimulation of the latter leads to dilatation of the arteries and a fall in pressure.

Impulses from the vasoconstrictor centre reach the sympathetic nerve centres situated in the lateral horns of the spinal cord, which form *spinal vasoconstrictor centres* connected with vessels in various parts of the body. These spinal centres are capable of producing a rise in blood pressure a certain time after it has fallen owing to dilatation of the arteries and arterioles following blocking of the vasoconstrictor centre in the medulla.

As well as those centres in the medulla oblongata and the spinal cord, there are nerve centres in the diencephalon and cerebral hemispheres that also influence the state of the vessels.

Stimulation of definite parts of the diencephalon in the region of the hypothalamus where the higher centres of the vegetative nervous

system lie, causes constriction of the arteries and arterioles and a rise in blood pressure.

#### REFLEX CONTROL OF VASCULAR TONE

It has already been mentioned that the arteries and arterioles are characterized by a constant tone maintained by impulses reaching them from the vasomotor centre via the sympathetic nerves. Arterial tone (in other words, a definite degree of constriction) is governed by the tone of the vasomotor centre located in the medulla oblongata, which in turn depends upon impulses conducted from peripheral receptors lying in certain vascular regions and on the surface of the body, and also upon humoral (chemical) stimuli that influence the nerve centre directly. Consequently, the tone of the vasomotor centre is both reflex and humoral in origin.

Following Chernigovsky's classification, reflex changes in the arterial tone, or *vascular reflexes*, may be divided into two groups: *proper* and *conjugated*. The proper vascular reflexes are produced by impulses originating in the receptors of the vessels themselves. Morphological studies have revealed a great number of these receptors; those concentrated in the aortic arch are of particular physiological importance and also those at the site where the carotid artery divides into its internal and external branches, (the carotid sinus). The parts of the vascular system abundantly supplied with receptors are known as main *vascular reflexogenic zones* (Fig. 39).

The receptors in the aortic arch are the endings of afferent fibres that form part of the *depressor* (aortic) nerve discovered by Cyon and Ludwig. Electrical stimulation of its central end results in a fall of blood pressure owing to a reflex increase in the tone of the vagal centre and a reflex inhibition in the tone of the vasoconstrictor centre. As a result, cardiac performance is inhibited while the vessels of the internal organs are dilated. If the vagal nerves are cut in an experimental animal (e. g. a rabbit), however, stimulation of the depressor nerve will cause only reflex vascular dilatation with no deceleration of cardiac rhythm.

In the reflexogenic zone of the carotid sinus there are receptors, that give rise to the afferent nerve fibres forming Hering's nerves, otherwise known as the *carotid sinus nerves* which enter the brain as part of the glossopharyngeal nerve.

The following experiment provides evidence of the role played by the carotid reflexogenic zone in the reflex control of the arterial pressure. All the branches of one of the carotid arteries are ligated above the site of its division into the external and internal arteries and a cannula is inserted into the common section and tied in place.

Introduction of blood under pressure through the cannula into the isolated carotid sinus is attended by a fall in pressure in the body arteries, as shown in Fig. 40. The decrease in general arterial pressure

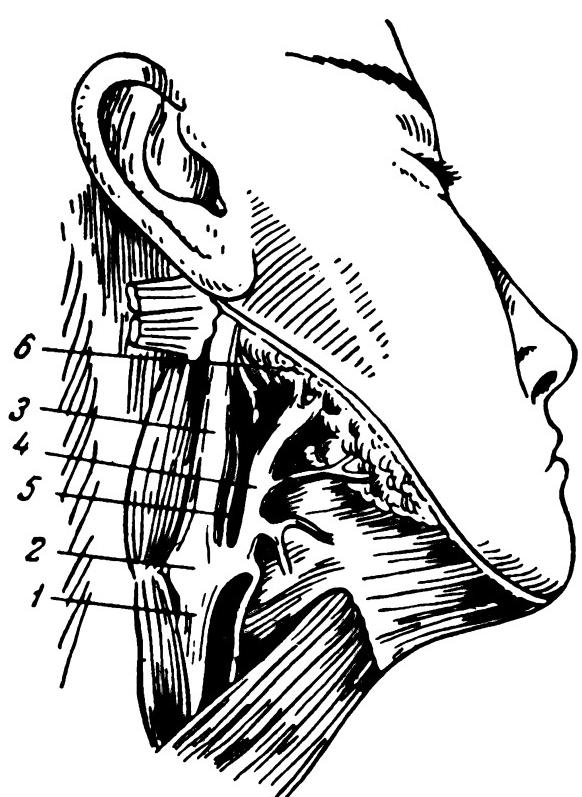


FIG. 39. Localization of the carotid sinus in man (after Heymans)

1 — common carotid artery; 2 — carotid sinus; 3 — internal carotid artery; 4 — external carotid artery; 5 — Hering's nerve; 6 — glossopharyngeal nerve

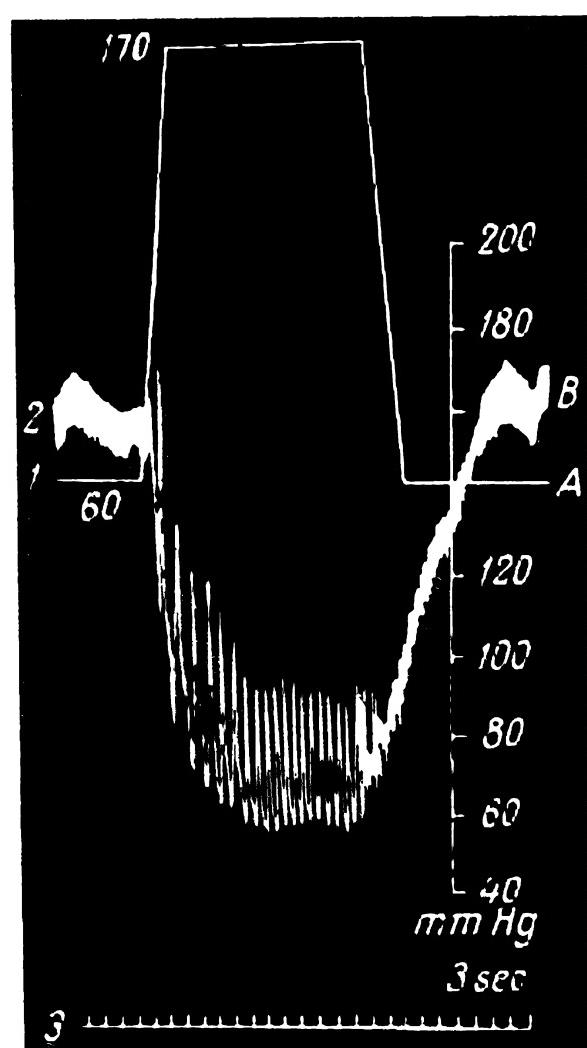
occurs because the distention of the carotid wall by the blood entering the artery under pressure stimulates the receptors of the carotid sinus, producing a reflex decrease in the tone of the vasoconstrictor centre and increase in the vagal tone. The stimulation mechanism of the receptors lying at the aortic arch is identical.

Since the receptors of the vascular reflexogenic zones are stimulated by a rise in blood pressure in a vessel they are called *pressoreceptors* or *baroreceptors*.

If the carotid sinus and aortic nerves are cut on both sides vascular hypertension results, i. e. the blood pressure in the carotid artery of a dog rises to 200 or 250 millimetres instead of the normal 100 to 120 millimetres of mercury.

A number of investigators have made electro-physiological analyses of baroceptor function (see Fig. 33). Each wave of elevated pressure in the aorta or carotid artery resulting from a ventricular systole is attended by a brief series of impulses from the aortic and carotid sinus receptors and reaching the central nervous system. With a persistent rise in blood pressure the production of impulses becomes continuous, causing a reflex lowering of the tone of the vasoconstrictor centre, leading in turn to dilatation of the vessels and a decrease in arterial pressure (*depressor reflex*).

The reflexogenic zones of the aorta and carotid sinus play an important part in the regulation of constant blood pressure. Under normal physiological conditions they prevent elevation of arterial pressure and for that reason are called the "restraints of blood pressure". (Blut-druck Zügler).



**FIG. 40. Influence of increased pressure in an isolated carotid sinus (after E. Moiseev's method) upon the arterial pressure of a dog (after Heymans)**

1 — pressure in carotid sinus; 2 — arterial pressure; 3 — time-interval marker (3 seconds). Figures on the right show arterial pressure values, figures on the left show carotid pressure values

The receptors of the vascular reflexogenic zones are also of importance in restoring pressure following its decrease. With a fall in the arterial pressure as a result, for example, of a decrease in the amount of blood in the body (following blood loss), of weakened cardiac activity, or of escape of blood into excessively dilated vessels of any large organ, the pressoreceptors in the aortic arch and carotid arteries are stimulated less intensely than with normal blood pressure. The "restricting" effect of the depressor and carotid sinus nerves on blood pressure weakens, the vessels become constricted, cardiac activity intensifies, and blood pressure rises a little.

Vascular reflexes can be produced by stimulating not only the receptors in the aortic arch and carotid sinus, but also those in the vessels in other parts of the body. An increase in pressure in the vessels of the lungs, intestine, or spleen, for example, is attended by reflex changes in blood pressure in other vascular regions.

Reflex regulation of blood pressure is achieved not only by stimulation of vascular pressoreceptors but also by stimulation of *chemoreceptors* that are sensitive to changes in the chemical composition of the blood. These chemoreceptors are concentrated in the *aortic body* (*glomulus aortae*), being lodged in the external coat of the ascending aorta, and in the *carotid body* (*glomulus caroticum*) situated at

the bifurcation of the common carotid artery. They are sensitive to carbon dioxide and to oxygen deficiency in the blood, and are also stimulated by carbon monoxide, cyanides, and nicotine. Impulses are transmitted from them along the afferent nerve fibres to the vaso-motor centre and causes an increase in its tone. As a result, vasoconstriction and a rise in blood pressure occur. The respiratory centre is stimulated at the same time (p.202).

Thus, stimulation of the aortic and carotid chemoreceptors produces *vascular pressor reflexes*, i.e. reflexes that cause a rise in pressure through constriction of the arterial bed, while stimulation of the pressoreceptors gives rise to *depressor reflexes*, i.e. to reflexes that cause a fall in blood pressure owing to dilatation of the arterial bed.

Chernigovsky and other authors have also revealed the presence of chemoreceptors in the vessels of the spleen, adrenals, kidneys, and bone marrow, which are sensitive to various chemical compounds circulating in the blood, e.g. acetylcholine, adrenaline, etc. Stimulation of chemoreceptors usually results in a rise in blood pressure.

The vascular baro- and chemoreceptors exert complex control of blood pressure and its rapid reflex compensation when, for any reason, it rises or falls beyond normal values.

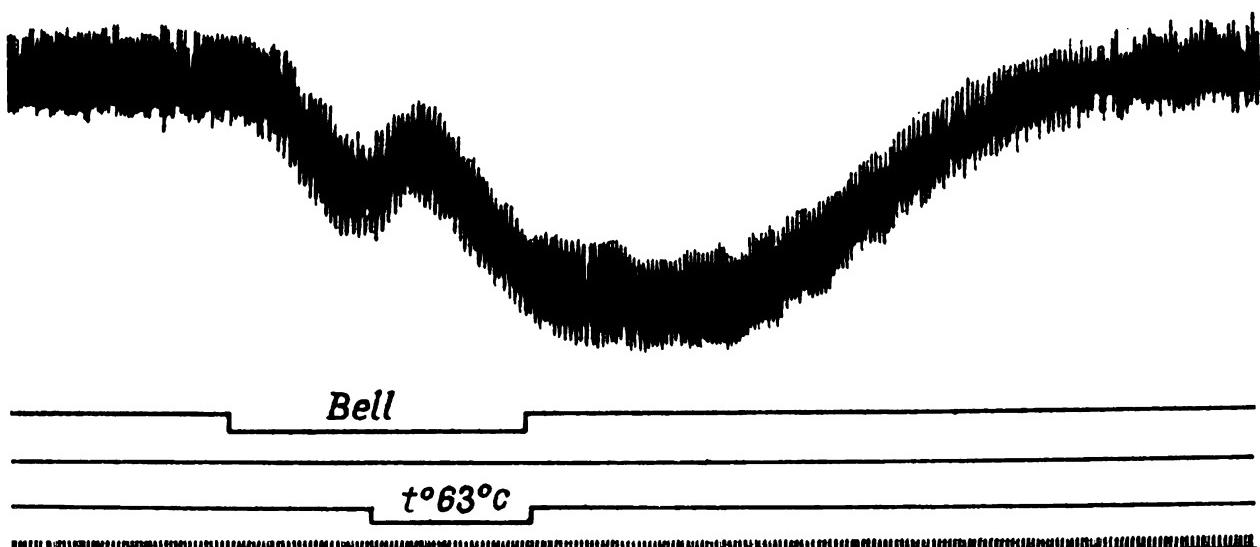
Conjugated vascular reflexes, showing mainly in a rise in arterial pressure, can be produced by stimulating receptors on the surface of the body. Pain stimuli cause a reflex constriction of vessels, in particular, those of the abdominal organs, which results in elevation of arterial pressure. The same effect can be produced in response to strong electrical stimulations of the central segment of any sectioned sensory nerve. Stimulation of the skin with cold also causes constriction of vessels, mainly of skin arterioles.

**Cortical control of vascular tone.** The influence of the cerebral cortex on the blood vessels was first demonstrated by stimulation of definite regions of the cortex.

Cortical vascular reactions have been studied in humans by means of conditioned reflexes. The occurrence of vasoconstriction or vasodilatation is judged from changes of the volume of the arm as recorded by plethysmography. With constriction of the vessels the amount of blood filling the organ, and, consequently, its volume, diminish. Conversely, with dilatation of the vessels the amount of blood and volume of the organ increase.

To study vascular reflexes by detecting changes in blood supply, the hand and forearm are placed in a *plethysmograph*, a hermetically sealed vessel connected to a manometer that records small pressure fluctuations. The volume of the limb in the plethysmograph changes with dilatation or constriction of the blood vessels, which produces changes in air or water pressure in the instrument, that are registered by the manometer and recorded as curves.

If a certain stimulus, for example, heating of a skin area with resultant reflex dilatation of the peripheral vessels, or either cooling



**FIG. 41.** Conditioned vasoconstrictor reflex produced in response to the sound of a bell combined with application of a pain thermal stimulus.

The plethysmogram tracings recorded from the arm are shown on the top; the intervals of conditioned and unconditioned stimulations are indicated on the bottom lines (after A. Pshonik)

of the skin or application of a pain stimulus, thus causing constriction of the peripheral vessels, is repeatedly applied in combination with an indifferent stimulus (sound, light, etc.), then after a period the indifferent stimulus alone will evoke a vascular reaction identical to that produced in response to the unconditioned thermal, cold, or pain stimulus applied simultaneously (Fig. 41).

Vascular response to a stimulus to which the vessels did not react before is effected by way of a conditioned reflex, i. e. through the cerebral cortex. In humans it is often accompanied by a corresponding feeling of cold, heat, or pain although no stimulus is applied to the skin.

The influence of the cerebral cortex is also demonstrated by the fact that the blood pressure rises in athletes before the start of exercise or event owing to changes in cardiac activity and vascular tone.

#### HUMORAL CONTROL OF FACTORS ON THE VESSELS

Certain humoral agents cause constriction of the vascular lumen, and others dilatation. The group of vasoconstrictors includes hormones secreted by the adrenal medulla (*adrenaline*) and the posterior lobe of the hypophysis (*vasopressin*).

Adrenaline causes constriction of the arteries and arterioles of the skin, skeletal muscles, abdominal organs, and lungs. According to certain data, the coronary and cerebral vessels respond by dilatation.

Vasopressin acts mainly on the arterioles and capillaries, causing their constriction.

Both adrenaline and vasopressin affect the vessels in very small concentrations. A  $1 \times 10^{-7}$  g/ml concentration of adrenaline in the blood,

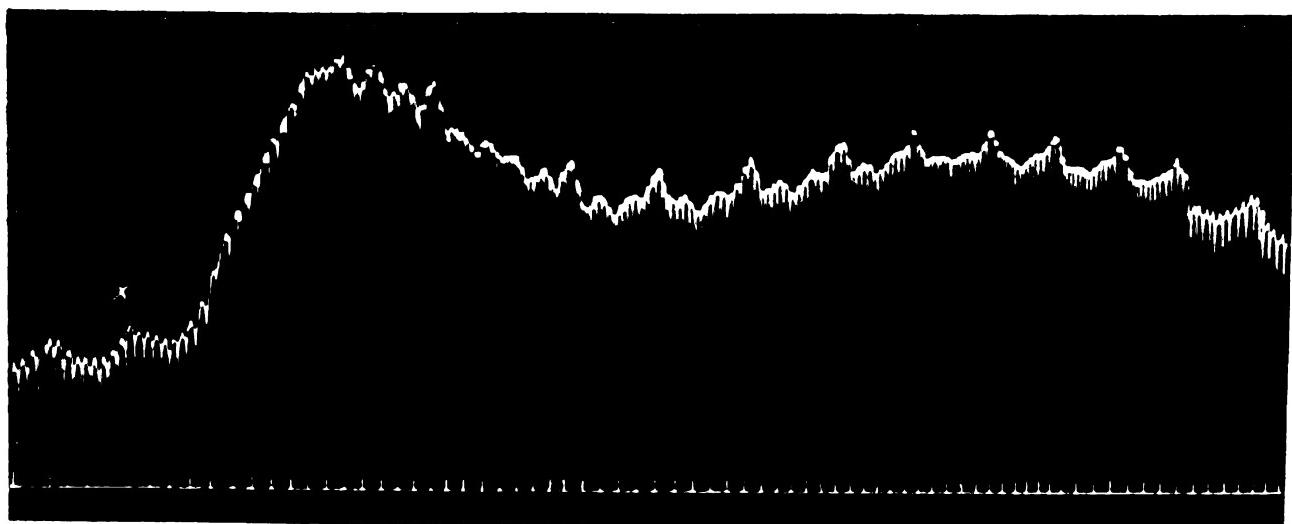


FIG. 42. The effect of adrenaline on the blood pressure in a dog  
 X — intravenous injection of one milligram of adrenaline into a dog with dissected vagus nerves

for example, induces constriction of vessels in warm-blooded animals. Owing to their vasoconstrictor effect they produce a sharp rise in blood pressure (Fig. 42).

A peculiar vasoconstrictor factor is formed in the kidneys, its production increasing markedly when their supply of blood diminishes. Therefore a persistent increase in blood pressure, owing to constriction of arterioles, occurs in a dog following partial compression of the renal arteries. To produce the rise in blood pressure clamps are applied to the renal arteries in such a way that their lumen is narrowed but does not close completely. As a result, constriction of arterioles occurs both in organs with normal innervation and in those denervated. Consequently, the effect depends not upon an increase in the tone of the vasoconstrictor centre, but upon the action of a humoral agent on the arterioles.

The substance formed in the kidneys has been named *renin*. It is an enzyme that does not by itself cause vasoconstriction. On entering the blood it acts upon one of the plasma globulins, *hypertensinogen*, and converts it into an active vasoconstrictor called *hypertensin*, *angiotonin* or *angiotensin* (hypertensin is a polypeptide with a much lower molecular weight than hypertensinogen).

With a normal blood supply to the kidneys, renin is produced in relatively small amounts, but large quantities are secreted when the renal vessels are compressed or when blood pressure falls along the entire vascular system. If the blood pressure of a dog is lowered by blood-letting, the kidneys liberate an increased amount of renin into the blood which facilitates the restoration of normal pressure by constriction of the vessels.

Under normal conditions, when only a small amount of renin is produced in the kidneys, hypertensin does not accumulate in

the blood because it is destroyed by the enzyme *hypertensinase* as soon as it is formed.

The discovery of renin and of the mechanism of its vasoconstrictive action was of great clinical interest as it explained the reason for high arterial pressure associated with certain diseases of the kidneys (*hypertension of renal origin*).

The *acetylcholine* formed in the endings of all parasympathetic nerves and sympathetic vasodilators is another substance that causes dilatation of the vessels. Along with other choline derivatives acetylcholine affects the small arteries. It is rapidly destroyed in the blood, so that it produces only a local effect under physiological conditions, i. e. it acts only at the site of its liberation by the nerve endings.

Another vasodilator is *histamine*, a substance formed in the walls of the stomach and intestine, and in many other organs, e. g. in the skin on its stimulation and in skeletal muscles during work. Histamine causes dilatation of the capillaries. Intravenous injection of one or two milligrams into a cat causes a sharp drop in arterial pressure owing to decrease in blood flow to the heart, although the force of cardiac performance remains the same; all the animal's blood accumulates in the distended capillaries, mainly in the abdomen (*histamine shock*).

Histamine takes part in the reaction of reddening of the skin in response to various stimulations, e. g. rubbing of the skin, application of heat, or ultra-violet irradiation.

In addition to histamine and acetylcholine, several other vasodilators are liberated or are formed in skeletal muscle during work, namely: adenosine triphosphoric acid and its decomposition products (adenylic acid in particular), lactic acid, and carbonic acid, etc.

Humoral vasoconstricting factors include *serotonin* (5-hydroxytryptamine) which is secreted in the intestinal mucosa and in some parts of the brain. It is also released by the disintegration of blood platelets during blood coagulation. The formation of serotonin is then of physiological importance because it causes vasoconstriction and hinders the escape of blood from an injured vessel.

#### CONTROL OF THE VOLUME OF CIRCULATING BLOOD

A normal blood supply to the organs and tissues requires there to be a definite relation between the volume of the circulating blood and the total capacity of the entire vascular system, which is achieved by means of several nerve and humoral control mechanisms. As an example, let us take the reactions of the organism to a decrease in the volume of circulating blood resulting from bleeding.

With loss of blood there is a diminution of the blood flow to the heart and a fall in arterial pressure, in response to which reactions

tending to restore it to normal take place. In the first place, reflex vasoconstriction occurs, leading to an increase of arterial pressure if not much blood has been lost. Then there is also a reflex intensification of the secretion of vasoconstrictive hormones, viz. adrenaline by the adrenals, and vasopressin by the hypophysis. That in turn leads to constriction of the vessels, mainly of the arterioles. A reflex increase in the rate and force of cardiac contraction also facilitates normalization of the lowered blood pressure. As a result of these neuro-humoral reactions arterial pressure can be maintained at an adequate level for some time following acute blood loss. The important part played in this by adrenaline and vasopressin is seen from the fact that death from blood loss occurs sooner if the adrenals and hypophysis are removed, than when they are present. The penetration of tissue fluid into the vessels, and the discharge into the blood stream of blood accumulated in the so-called *blood reservoirs*, also help to maintain blood pressure following an acute blood loss by bringing about an increase in the volume of circulating blood and so raising arterial pressure.

There is a definite limit, however, beyond which no regulatory adjustments (whether constriction of the vessels, mobilization of blood from the reservoirs, or intensified cardiac performance) are capable of maintaining blood pressure at the normal level; if the organism loses about half its total volume of blood, pressure of the blood falls rapidly and may drop to zero, the condition terminating in death.

**Blood reservoirs (depots).** About 45 to 50 per cent of all the blood in the human organism is accumulated in the blood reservoirs (the spleen, liver, subcutaneous vascular network, and lungs) when the body is at rest. Five hundred millilitres of blood is stored in the spleen and may be almost entirely excluded from the circulation. Blood circulates in the vessels of the liver and in the vascular network of the skin (which may hold as much as one litre in man) at a much slower rate (ten to twenty times slower) than in other vessels. Hence blood is detained in these organs and they serve as reservoirs or *blood depots*.

The reservoir function of the *spleen* is conditioned by the peculiar structure of its vessels. Blood from the capillaries first enters the venous sinuses and then passes into the veins. The diameter of the sinuses differs according to the amount of blood filling them and varies between 12 and 40 microns. At the junction of the sinus with the vein there is a sphincter whose contraction detains blood in the sinus, so that its diameter increases. Blood plasma penetrates through the sinus wall into the tissue fluid; as a result the concentration of formed elements in the blood contained in the spleen is higher than that in the vessels of other organs. With relaxation of the sphincters blood easily escapes from the splenic venous sinuses into the veins and enters the systemic circulation.

The assumption that the spleen controls the volume of circulating blood had been made in the last century by Sechenov, Botkin, and Tarkhanov. The effect of different conditions (suffocation, blood loss, muscular activity, etc.) on the volume of the spleen was studied in detail by Barcroft by X-ray experiments on cats.

The spleen cannot normally be examined by X-rays as it gives no discernible shadow. To overcome this difficulty, a large number of metal tacks are attached to its surface in such a way that they are fixed only to its capsule and do not injure the parenchyma or smooth muscles, and do not impair contraction and swelling. Then the operative wound is sutured and the animal is allowed to recover. The size of the spleen can then be determined on X-ray from the arrangement of the tacks. In other experiments a celluloid window was stitched into the abdominal wall so that the changes in the size and contours of the spleen could be observed.

The mobilization of splenic blood augments the transport of oxygen since it contains more erythrocytes and is 15 per cent richer in haemoglobin than the blood circulating in the vessels.

With a decrease in the oxygen content of the blood, the spleen contracts reflexly and squeezes out an additional amount of blood. The contraction occurs in the following conditions: 1) blood loss; 2) decreased atmospheric pressure, or lowered partial oxygen pressure; 3) carbon monoxide poisoning; 4) chloroform or ether anaesthesia; 5) muscular activity, and other similar conditions.

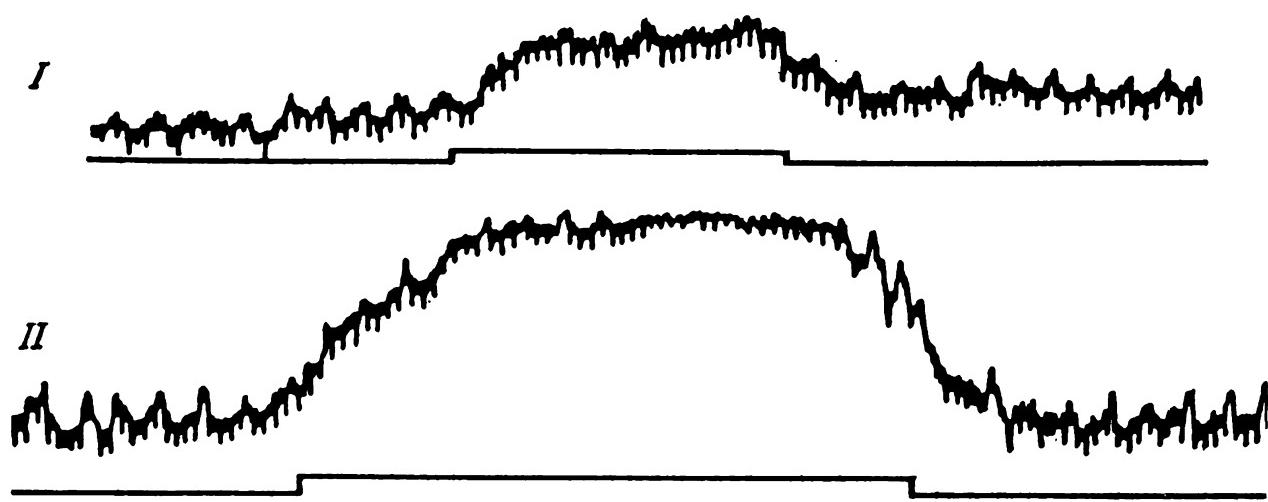
When the body is at rest, the spleen is large and rich in blood, and consequently the amount of circulating blood is reduced.

Another important blood reservoir is the *liver*. The walls of the large branches of the hepatic veins contain muscular bundles forming sphincters whose contraction narrows the orifices of the veins and blocks the outflow of blood from the liver. In that way blood is held back and the liver becomes engorged with it. This blood is not, however, excluded from the circulation, as with the spleen, but its flow is retarded by the contraction of the hepatic vein sphincters.

The blood filling the spleen and liver and, consequently, their reservoir function, is regulated by reflexes.

**Changes in the distribution of circulating blood.** A redistribution of circulating blood occurs when a system of organs is working. Blood supply to the working organs is increased at the expense of a diminution of the flow to other parts of the body. It has been found that the vessels of the internal organs and of the skin and skeletal muscles produce reactions opposite in character, which can be illustrated by the fact that blood flow to the alimentary organs increases during a digestion period owing to dilatation of the vessels supplying the entire area innervated by *n. splanchnicus*, while the blood supply to the skin and skeletal muscles decreases.

The supply of blood to the brain intensifies during mental work, which can be demonstrated experimentally as follows: a subject is



**FIG. 43. Changes in the blood filling of the head of an individual (determined from changes in the weight of his head) solving problems in arithmetic (after E. Babsky et al.)**

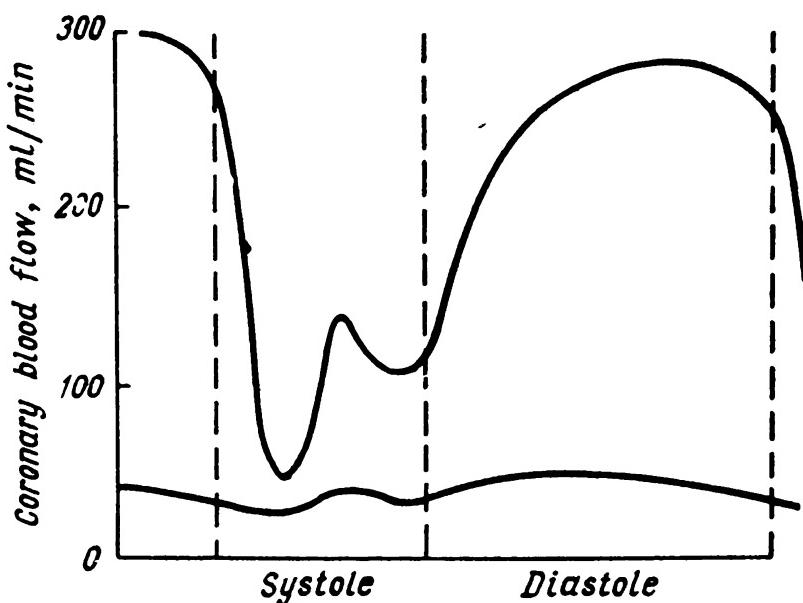
Top tracings recorded during multiplication of two-digit numbers; bottom tracings — during multiplication of three-digit numbers

placed on a balanced horizontal platform and asked to solve a problem in mental arithmetic; because of the increased flow of blood to the brain, the head end of the platform will descend. Similar experiments have been conducted employing electric scales placed under the head of a subject lying on a couch. While he is solving an arithmetical problem the volume of blood in the brain increases owing to dilatation of the vessels and, consequently, the weight of the head increases (Fig. 43).

Intensified muscular exercise is attended by constriction of the vessels of the digestive organs and by an increase in blood flow to the skeletal muscles. The increase in flow is facilitated by a local vasodilator effect caused by various metabolites produced in the working muscles during contraction (lactic and carbonic acids, adenylic acid derivatives, histamine, and acetylcholine), as well as by reflex vasodilatation. Work performed with one hand, for instance, is accompanied by dilatation of the vessels not only in that hand, but also in the other one, and in the legs, which can be demonstrated experimentally by means of a plethysmograph.

Dilatation of the arterioles and capillaries of the skin with a rise of the environmental temperature is another blood redistribution reaction, and occurs in response to stimulation of the skin *thermoreceptors*. The physiological significance of the reaction is the intensification of heat loss by the blood flowing along the dilated small vessels of the body surface.

Redistribution of blood also occurs with a change from a horizontal to a vertical position. Venous flow from the lower limbs becomes difficult, so that the amount of blood entering the heart by the inferior vena cava is reduced sometimes to one-tenth or one-



**FIG. 44.** Blood flow through the left (top) and right (bottom) coronary arteries (after A. Guyton)

fifth of the normal inflow, the decrease in the size of the heart can be clearly seen by X-rays.

## CIRCULATION IN THE HEART AND LUNGS

### CIRCULATION IN THE CORONARY VESSELS OF THE HEART

The supply of blood to the heart is ensured by the *coronary* vessels, and occurs mainly during a diastole, in contrast to other vessels. Contraction of the myocardium during the period of ventricular tension compresses the small arteries lying within it to such an extent that blood flow in the coronaries is sharply reduced (Fig. 44). Some blood from the cardiac veins enters the coronary sinus which empties into the right atrium. The sinus receives blood mainly from the veins of the left ventricle, around 75 to 90 per cent. The greater amount of the blood flowing from the myocardium of the interatrial septum and right ventricle along the numerous minute thebesian vessels drains into the right ventricle.

From 200 to 250 millilitres of blood flow through the coronaries of a human being per minute, which is about 4 to 6 per cent of the minute volume of the heart. During physical exertion coronary flow may rise to three or four litres per minute.

Ligation of the coronary vessels in experimental animals, or their severe constriction (spasm) or occlusion by a thrombus in human beings, leads to disorders in cardiac activity, weakening of contractions and disturbance of rhythm, and even to sudden arrest during a diastole.

A technique to *catheterize* the coronary sinus in humans and animals has been elaborated, involving the introduction of a thin rubber catheter passed through a peripheral vein. Myocardial consumption of various substances can be determined by comparing their content in samples of blood obtained simultaneously from

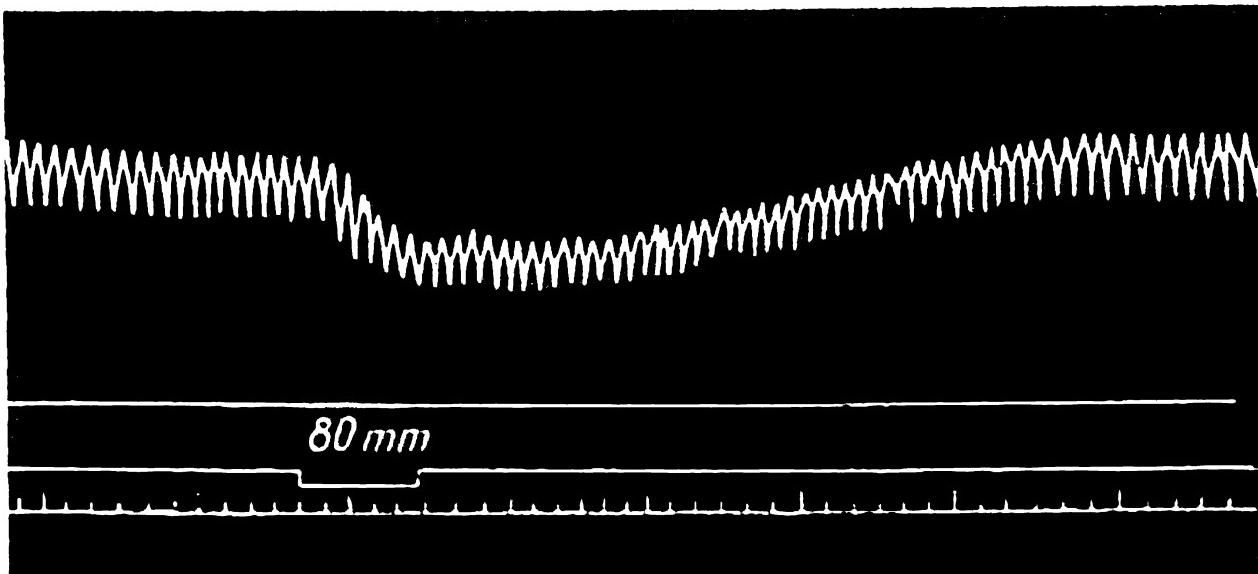
an artery and from the coronary sinus. It was established in this way that the percentage of oxygen derived from the blood by the heart is higher than in other organs. A deficient supply of oxygen results in disturbance of the work of the heart and the appearance of pain. These phenomena are not encountered in normal physiological conditions because a decrease in the blood oxygen content leads to dilatation of the coronaries and an increase in blood flow to the heart, which may double when respiration is suppressed. Coronary circulation is controlled by nervous and humoral mechanisms.

Since stimulation of the parasympathetic and sympathetic nerves, and the introduction of various substances, both, as a rule, cause changes in coronary blood flow and in myocardial activity, recognition of the character of their influence on the coronary vessels is complicated. Consequently, it is often difficult to judge what factor is responsible for the change in blood flow through the coronaries, whether it is changes in cardiac performance, and so in myocardial metabolism, or the direct influence exerted on the walls of the cardiac vessels by the factor under test. That explains the many contradictory conclusions drawn by various researchers; some claim, for example, that the sympathetic nerves cause dilatation of the coronary vessels, while others assume that they are responsible for coronary constriction.

#### PULMONARY CIRCULATION

The lungs are supplied with blood from both circuits: the pulmonary circulation conveys venous blood through the pulmonary artery to the capillaries of the pulmonary alveoli for gas exchange, while the systemic circulation brings arterial blood through the bronchial arteries to feed pulmonary tissue. The vessels of the two circulations are not sharply isolated one from another in the lungs, but form anastomoses in the region of the capillary bed. Blood flows in only one direction in these anastomoses, from the capillaries of the bronchial arteries to the capillaries of the pulmonary arteries. The surface of the capillary network of the pulmonary circulation has an area of about 140 square metres. Blood particles pass through the lungs in approximately six seconds, remaining in the capillaries, where the interchange of gases occurs, for an interval of 0.7 of a second.

The resistance to blood flow of the pulmonary vessels is about 10 per cent of that encountered in systemic circulation, which is mainly due to the wide calibre of the pulmonary arterioles (their diameter is up to 80 microns, while that of systemic arterioles does not exceed 12 microns). Since the right ventricle encounters a lower resistance, it bears a lighter load, and the pressure it develops is much less than that in the left ventricle.



**FIG. 45. Drop in carotid blood pressure with a rise in pressure in the pulmonary vessels (after V. Parin)**

Top tracings — recording of carotid blood pressure; second line — zero level of blood pressure; third line — shows the moment when the pressure in the pulmonary veins is raised to 80 millimetres mercury; bottom line — time-interval marker

The systolic pressure in the pulmonary artery of man, as determined by catheterization or puncture of the pulmonary artery, is between 25 and 30 millimetres of mercury. The diastolic pressure varies between five and ten millimetres, and the pulse difference between 15 and 20 millimetres. The mean pressure in the pulmonary artery is one-fifth to one-sixth that in the aorta.

Vasoconstrictor innervation of the lungs is supplied from the upper segments of the thoracic portion of the spinal cord, mainly from the third to seventh segments, and is part of the sympathetic system. Stimulation of the sympathetic stellate ganglion causes a marked rise in pressure within the pulmonary arteries by increasing the tone of the vessels of the pulmonary circuit. Adrenaline renders a similar effect; acetylcholine, on the contrary, causes dilatation.

The capacity of the pulmonary vascular bed may increase or decrease. For instance, the marked increase of resistance to blood flow in the vessels of the systemic circulation caused by the introduction of adrenaline is accompanied by an increase in the amount of blood in the lungs.

Owing to the variable capacity of the pulmonary vessels, the blood in the lungs may vary between 10 and 25 per cent of the total amount of blood in the organism. Thus the lungs are a blood reservoir of the body.

The reflex weakening of cardiac activity, and the dilatation of the vessels of the systemic circuit occurring in response to a rise in blood pressure in the systemic circulation as a reflex from the vascular reflexogenic zones, are attended by a simultaneous reflex increase in the blood filling the pulmonary circuit. So pressure is compensated, and a redistribution of blood between the two circulations occurs.

As well as reflexes arising from the vascular receptors of the systemic circulation, which control the capacity of the pulmonary circuit, there is also the opposite reflex from the pulmonary vessels to those of the systemic circuit described by Schwiegk and Parin (Fig. 45). This reflex occurs with an increase in pressure in the pulmonary vessels, when the pulmonary circuit is congested with blood, and causes deceleration of cardiac performance, vasodilation in the systemic circuit, and a swelling of the spleen, all of which leads to an increase in the amount of blood in the systemic circulation and a corresponding decrease in the pulmonary circulation. The redistribution of blood prevents its congestion in the lungs; the physiological importance of the reflex is that it relieves the work of the heart and normalizes circulation.

#### THE LYMPH AND ITS CIRCULATION

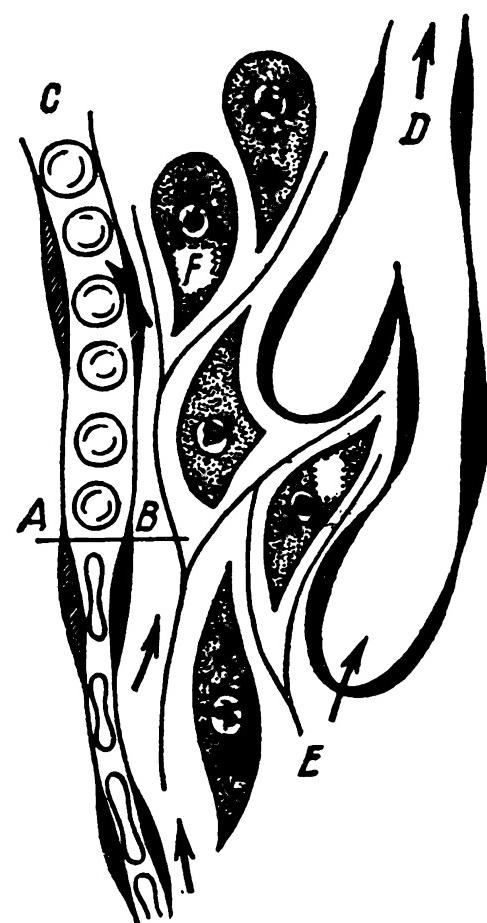
In addition to the system of blood vessels the body contains a system of lymphatic vessels, which begins with a branching network of closed capillaries (Fig. 46) whose walls are extremely permeable and capable of absorbing colloidal solutions and suspensions. The lymphatic capillaries drain into lymphatic vessels along which a fluid, *lymph*, flows toward two large lymphatic ducts, the cervical and thoracic, which in turn empty into the subclavian veins.

As distinct from the blood vessels, which carry blood both to the body tissues and away from them, the lymphatic vessels serve only to drain off lymph, i. e. to return to the blood fluid exuded into the tissues. They are thus a sort of drainage system that removes excess *tissue*, or *interstitial*, *fluid* accumulating in the organs.

It is extremely important that the lymph flowing from the tissues passes to the veins via biological filters, the *lymph nodes*. Certain foreign particles that have penetrated into the organism, e. g. bacteria, dust, etc., are detained here and do not enter the blood. These particles pass from the tissues into the lymphatics and not into the blood capillaries because the walls of the former are much more permeable.

#### COMPOSITION AND PROPERTIES OF LYMPH

The lymph collected from lymphatic ducts during fasting, or after a meal poor in fats, is a colourless, almost transparent, fluid differing from blood plasma in its protein content, which is about twice as high in plasma as in lymph. Lymph obtained from the thoracic duct and from the intestinal lymphatics six to eight hours after a meal rich in fats is cloudy and milky because it contains emulsified fats absorbed in the intestine. Since lymph contains less protein than blood, its viscosity is less and its specific gravity lower. Lymph has an alkaline reaction.



**FIG. 46. Schematic representation of the relationship between the lymphatic and blood capillaries (after D. Zhdanov)**

A-B — site where the arterial segment of the capillary is continuous with the venous segment; C — blood capillary; D — lymphatic capillary; E — connective-tissue fibres; F — cells

Because it contains fibrinogen, lymph is capable of coagulation, forming a loose, slightly yellowish clot.

The lymph draining from different organs and tissues varies in composition according to the peculiarities of their metabolism and activity. Lymph from the liver, for instance, contains much more protein than that from the limbs. The lymph in the lymphatic vessels of the endocrine glands contains hormones.

There are usually no erythrocytes in the lymph and only a very small number of granular leucocytes that have escaped from the blood capillaries through their endothelial wall and then from tissue spaces into the lymphatic capillaries. With injury to blood capillaries, particularly on exposure to ionizing radiation, the permeability of their walls increases and great numbers of erythrocytes and granular leucocytes may be present in the lymph.

The lymph of the thoracic duct contains a large number of lymphocytes (between 2,000 and 20,000 per cubic millimetre in man, according to some authors), since they are produced in the lymph nodes and are carried to the blood with the lymph flow.

#### PRODUCTION OF LYMPH

The production of lymph is associated with the passage of water, and certain substances dissolved in the blood plasma, from the

blood capillaries into the tissues, and thence into the lymphatic capillaries.

The first explanation of the mechanism of lymph formation was offered in the fifties of the last century by Ludwig, who assumed it to be due to the filtration of fluid through the capillary wall, the driving force being the difference between the hydrostatic pressure within the capillary and outside it. Evidence in favour of his conception is offered by the fact that with a decrease in blood pressure, due to blood letting for example, the production of lymph is delayed or even arrested. If the veins leaving any organ are compressed, however, the resulting sharp rise in the blood pressure within the capillaries causes an intensification of lymph production.

According to current conceptions, the walls of blood capillaries are a semi-permeable membrane with ultra-microscopic pores through which the filtration occurs. The size of the pores differs with the organs and, consequently, the capillaries vary in permeability. The walls of liver capillaries, for example, are more permeable than those in the skeletal muscles, which explains the fact that more than half the total amount of lymph draining through the thoracic duct is produced in the liver.

The permeability of blood capillaries may change with various physiological conditions, e. g. under the influence of secretion into the blood of the so-called capillary toxins (histamine and others).

The filtration theory of lymph formation was further developed by Starling, who showed that not only is the difference in hydrostatic pressure between the blood capillaries and tissues responsible for the process, but that an important role is also played by the difference in osmotic pressure between the blood and tissue fluid. The higher osmotic pressure of blood is due to the capillary wall being non-permeable for plasma proteins. The osmotic pressure of plasma due to proteins (colloido-osmotic or oncotic pressure, p. 63) facilitates the retention of water in capillary blood. Thus, the hydrostatic pressure of the blood in the capillaries facilitates, while the oncotic pressure of blood plasma hinders, the filtration of fluid through the walls of the capillaries and the production of lymph. This influence of oncotic pressure on lymph formation is particularly marked in those organs where the capillaries are not very permeable and the tissue fluid and lymph contain only a small amount of proteins (the muscles and skin). In the liver, where the capillaries are more permeable and the lymph is rich in proteins, the difference in colloido-osmotic pressure is slight, so that production of lymph is more intense and depends chiefly on the general blood pressure.

Since the osmotic pressure of blood proteins hinders lymph formation, while higher hydrostatic pressure stimulates it, the force of the filtration pressure can be estimated by subtracting the differ-

ence in colloid-osmotic pressure between the blood and lymph from the value of the blood pressure in the capillaries.

According to certain data, fluid filtration occurs only at the arterial end of a blood capillary, i. e. in its initial segment, because the blood pressure there exceeds the oncotic pressure of the plasma protein. A reverse process is encountered at the venous end of the capillary, the fluid passing into the capillaries from the tissue, which is explained by the fact that blood pressure falls by ten to fifteen millimetres of mercury as it flows from the arterial to the venous end, while the oncotic pressure increases owing to a certain degree of blood concentration.

The passage of fluid from the blood into the tissues is intensified with a fall in the colloid-osmotic pressure of the blood. That occurs, for example, if the vessels of an organ are washed out with Ringer's solution containing no colloids, and the organ rapidly becomes oedematous as a result. Intensification of lymph production may be encountered following intravenous injection of a large amount of physiological solution; but neither intensified lymph formation nor tissue oedema are observed if 7 per cent of dextran (a polysaccharide, p. 62) or casein (a protein preparation) is added to the solution, as these substances, being colloids, do not penetrate the vascular wall.

A rise in the osmotic pressure of the tissue fluid and of the lymph itself is another factor contributing to the production of lymph, which becomes particularly important when dissimilation products pass into the tissue fluid and lymph in great amounts. Most metabolites have a relatively small molecular weight, and because of that they cause an increase in osmotic pressure in the fluid. With the dissociation of a large molecule into a number of small ones osmotic pressure rises since it depends upon the number of molecules and ions. A particularly sharp rise in the osmotic pressure of tissue fluid and lymph occurs in a strenuously working organ in which dissimilation processes are intensified. The rise causes water to pass into the tissues from the blood, so facilitating lymph formation.

The production of lymph is promoted by certain substances, known as *lymphagogues*, introduced into the blood. Their effect cannot be attributed to relatively simple physico-chemical phenomena. Extracts of crawfish, leeches, and wild strawberries, and peptones, histamine, etc. cause an effect promoting lymph production even when introduced in negligible amounts that cause no change in the osmotic pressure of the blood plasma. There is usually no concurrent raising of blood pressure, which often even falls, yet the production of lymph intensifies.

The mechanism of these lymphogenous agents consists in their increasing the permeability of the capillary wall, an effect similar to that of factors causing inflammation (bacterial toxins, burns,

etc.), which also promote capillary permeability leading to the formation of an inflammatory exudate.

While noting the importance of filtration in the production of lymph, we must stress that the endothelial wall of capillaries is not a passive membrane through which blood plasma filters. This is obvious if only because the substances passing across it from the blood to the lymph vary with the different tissues. The capillary walls possess selective permeability which is particularly marked in the brain where they obstruct the passage of certain substances that easily penetrate the capillary walls in other organs.

#### MECHANISM OF LYMPH MOVEMENT

Under normal conditions there is an equilibrium in the organism between the rate of lymph formation and the rate of lymph flow from the tissues. Lymph flows from the lymphatic capillaries along the vessels that coalesce to form the two large lymphatic ducts draining into the veins. Thus, fluid that has escaped from the blood in the capillaries returns to the blood stream carrying with it products of cell metabolism.

A definite role in the flow of lymph is played by rhythmical contractions of the walls of certain lymphatic vessels, contractions that occur at a rate of eight to ten, or even twenty-two per minute (as reported by individual researchers). And owing to the presence of valves in the lymphatics, the flow takes place in one direction only.

Some lower vertebrates, frogs for example, have special organs, *lymph hearts*, in their lymphatic system, that act as pumps effecting the movement of lymph.

Negative pressure in the chest (p. 173) and the increase in volume of the chest during inspiration, which lead to dilatation of the thoracic lymphatic duct and aspiration of lymph from the lymphatic vessels, are of great importance in the movement of lymph.

Flexion and extension of the limbs during work or walking promote the movement of the lymph, as of venous blood. The lymphatics are compressed by the muscular contraction, which causes the lymph to move in one direction only.

The amount of lymph returning to the blood through the thoracic duct in the course of a day is between 1,200 and 1,600 millilitres in man.

The rate of the lymph flow is very low; in the cervical lymphatic vessel of a horse, for example, it varies between 240 and 300 millimetres per minute (blood covers the same distance in the veins in one second). Zhdanov determined the rate of lymph flow in the main human lymphatic vessels through study of a man who had sustained an injury to the thoracic duct. Stained lymph was discharged from the thoracic duct three minutes after two millilitres

of a dye solution had been introduced into the superficial inguinal lymph node.

Morphological research has revealed nerve fibres leading to the large lymphatic vessels, while physiological experiments have demonstrated the effect of sympathetic nerves on the lymph flow. Rushnyak and co-workers, for instance, observed that on stimulation of the sympathetic trunk contractions and spasm of the lymphatics were so severe as to stop lymph flow. It has been demonstrated that lymph flow is changed by reflexes to pain stimulation, raising of pressure in the carotid sinus, and stimulation of the receptors in many internal organs.

## Chapter 5

# RESPIRATION

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Respiration is the complex of processes by which an organism meets its requirements of oxygen and eliminates carbon dioxide.

In man and the higher animals it comprises the following processes: 1) exchange of air between the external environment and the pulmonary alveoli (*external respiration* or *lung ventilation*) ; 2) exchange of gases between the alveolar air and the blood flowing along the pulmonary capillaries (*diffusion of gases in the lungs*) ; 3) transport of gases by the blood; 4) exchange of gases between blood and tissues through the tissue capillaries (*diffusion of gases in the tissues*) ; 5) consumption of oxygen by cells and the elimination of carbon dioxide (*cell or internal respiration*).

The physiology of respiration studies the first four of these processes, the way they are regulated and the peculiarities of their course under various conditions. Cell respiration is mainly studied in biochemistry, which examines the oxidation processes in tissues by which intracellular substances, rich in energy, are broken down and the energy thus released.

### EXTERNAL RESPIRATION

External respiration, i. e. the exchange of air between the pulmonary alveoli and the environment, occurs as a result of rhythmical respiratory movements of the chest. With each inspiration the volume of the thorax and of the lungs is increased, the pressure within them falls, and air enters the alveoli by the air passages.

With expiration, the volume of the chest is reduced, the lungs partly collapse, pressure in them increases, and the air in them is discharged into the environment.

The interchange of gases between air and blood takes place in the alveoli. The blood in the capillaries entwining the alveoli absorbs oxygen from the air in them (alveolar air) and gives up carbon dioxide. The composition of the air in the alveoli is continuously renewed through respiration. Air rich in oxygen enters them during inspiration and air containing a large amount of carbon dioxide is discharged from them on expiration. A definite level of oxygen and carbon dioxide is thus maintained in the alveolar air and blood.

#### MECHANISM OF INSPIRATION

*Inhalation*, or breathing in, occurs owing to an increase in the volume of the thoracic cavity in three dimensions, vertical, sagittal, and frontal, which is due to elevation of the ribs and a downward movement of the diaphragm (Fig. 47).

The ribs are joined to the sternum by cartilages and to the spinal column at two points, the head of the rib being attached to the body of the vertebra, and its tubercle to the lateral process of the vertebra. On expiration or breathing out the ribs are pulled downward; on inspiration they move upward, their position becoming more horizontal and the lower end of the sternum moving forward, so that the transverse and longitudinal dimensions of the thorax increase.

The ribs are elevated by contraction of the *external intercostal* (mm. *intercostales externi*) and *intercartilaginous* (mm. *intercartilaginei*) muscles. The former pass from one rib to another obliquely, i. e. forward and downward.

The ribs act as levers of the second order with the pivot at their articulation with the spinal column (Fig. 48, points A and C). It would seem that on contraction the external intercostal muscles would bring the ribs closer to each other, but since the moment of force is greater at the lower attachment of the muscle (D) than at the upper (B) (because lever C-D is longer), their contraction causes the ribs to rise.

During inspiration the muscular fibres of the diaphragm contract and its cupula becomes flatter and descends, displacing the abdominal organs downward, to the sides, and forward; the volume of the thoracic cavity is increased, especially in the vertical direction.

Electrophysiological studies of the various respiratory muscles have shown that bioelectrical oscillations (action potentials) occur first in the diaphragm and then in the intercostal muscles.

During the first months after birth, respiratory movements are maintained mainly by the contraction of the diaphragm. Because

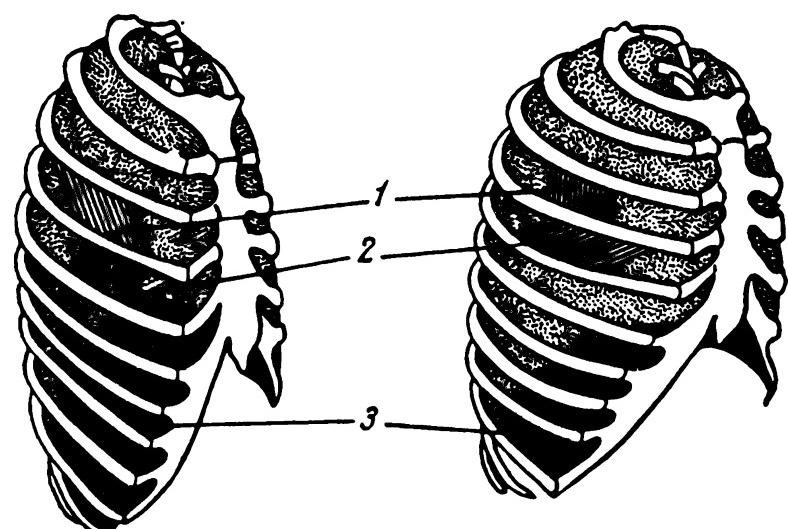


FIG. 47. Schematic representation of the position of the thoracic cage and diaphragm in expiration (left) and inspiration (right).

1 — external intercostal muscles; 2 — internal intercostal muscles; 3 — diaphragm

of that, a kitten dies if its diaphragm is paralysed by cutting the phrenic nerves.

In different people respiration is effected mainly either by the intercostal muscles (the *costal or thoracic type of respiration*) or by the diaphragm (*diaphragmatic or abdominal type of respiration*), depending upon their age and sex, or upon their clothes or working conditions.

The type of respiration is not strictly constant and may be adjusted to the conditions of the moment. When a heavy load is carried on the back, for instance, the thorax supports it and for that reason is held rigid with the spinal column by the muscles of the trunk and intercostal spaces; respiration is effected solely by the diaphragm. During pregnancy downward movement of the diaphragm is hampered so that costal respiration prevails.

With forced or intensive breathing, in dyspnoea for example, a number of *additional or accessory respiratory muscles* come into play, that raise the upper ribs (mm. sternocleidomastoidei and mm. scaleni) and draw the shoulder girdle and shoulders back (mm. trapezi, mm. rhomboidei, and mm. levatores scapulae).

The accessory muscles also include the following muscles that can also raise the ribs: mm. pectorales major et minor, and mm. serrati anterior.

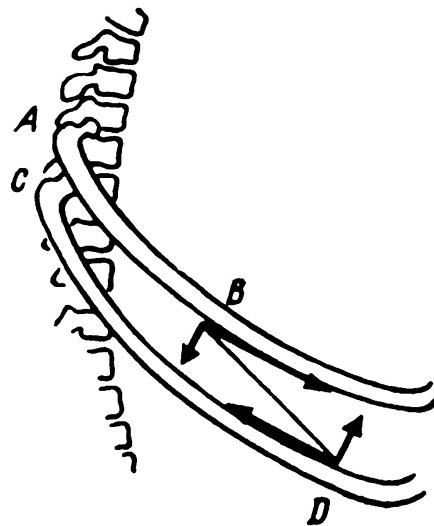


FIG. 48. Mechanism of rib movements with inspiration (discussed in the text)

### MECHANISM OF EXPIRATION

During inspiration the respiratory muscles have to overcome a number of forces: viz. 1) the weight of the thorax being raised; 2) the elastic resistance of the costal cartilages; 3) the resistance of the abdominal walls and abdominal organs being depressed by the descending cupula of the diaphragm. As soon as an inspiration ends and the respiratory muscles relax, the ribs descend and the diaphragm rises due to those forces, and the volume of the cavity is thereby reduced. Thus, expiration or breathing out is usually a passive act not involving the muscles.

With forcible expiration the forces that reduce the volume of the thorax are augmented by contraction of the internal intercostal and inferior posterior serratus muscles and abdominal muscles.

The internal intercostal muscles are formed of fibres lying in a direction opposite to those of the external intercostal muscles, i. e. backward and downward, so that when they contract the ribs descend.

Contraction of the abdominal muscles pushes the abdominal organs downward and the diaphragmatic cupula upwards.

### CHANGES IN THE LUNG VOLUME DURING RESPIRATION

The lungs, enclosed in the thorax, are separated from its walls by the pleural cavity or space, i. e. the narrow space formed between the parietal pleura lining the inner surface of the thoracic cage and the visceral pleura covering the outer surface of the lungs. During inspiration, when the thoracic cavity is enlarged, pressure in the pleural space is reduced and the volume of the lungs increases while the pressure inside them falls. As a result, air enters them along the air passages.

On expiration, when the cavity of the thorax becomes smaller, pressure in the pleural space increases slightly and the expanded pulmonary tissue shrinks; the pressure in the lungs therefore increases and air is expelled.

Thus, the changes in the volume of the lungs occur passively through changes in the volume of the thoracic cavity and pressure fluctuations in the pleural space and within the lungs.

The mechanism of the changes occurring in the volume of the lungs during breathing can be demonstrated by means of *Donders' model*.

Donders' model consists (Fig. 49) of a glass bell-jar with a rubber bottom and a stoppered top opening through which a glass tube is inserted. The end of the tube inside the jar is introduced into the trachea of a small animal (a rat or a rabbit) removed together with the bronchi and lungs. The lungs communicate with the atmosphere, the upper end of the tube projecting from the stopper. The pressure in the jar can be measured with a manometer connected

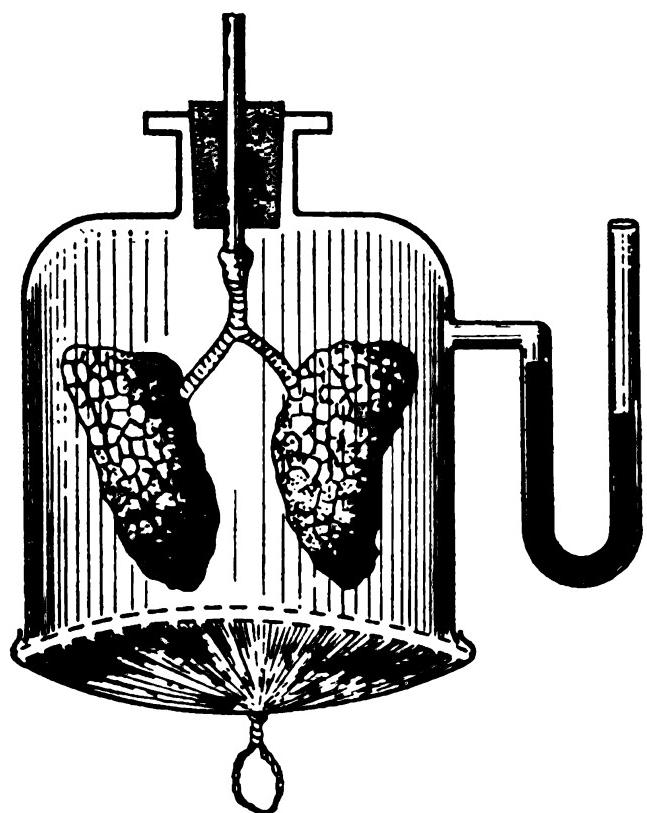


FIG. 49. Donders' model for demonstration of the mechanism of the respiratory act (discussed in the text)

to a glass tube fixed into the jar wall. When the rubber bottom of the jar is pulled down, its volume increases and the pressure inside it falls below that of the atmosphere. That causes expansion of the pulmonary tissue and atmospheric air flows into the lungs.

The pressure of the air in the jar between its walls and the external surface of the lungs, however, remains a little below that of the atmosphere, since the resilience of the pulmonary tissue resists expansion. When the rubber bottom of the jar is released it returns

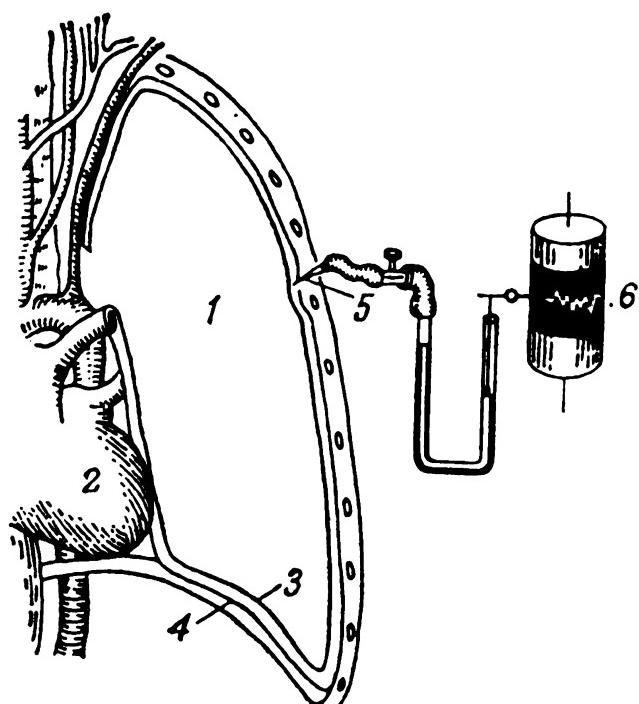


FIG. 50. Method for recording intrapleural pressure (schematic representation)

1 — lungs; 2 — heart; 3 — visceral pleura; 4 — parietal pleura; 5 — needle; 6 — kymograph

to its place; the volume of the jar decreases and the action of the force expanding the lungs ceases. Owing to its elasticity the pulmonary tissue collapses, pressure in the lungs rises, and air is expelled.

Donders' model demonstrates that the immediate cause of lung expansion during inspiration and of lung collapse during expiration are changes in the volume of the thoracic cavity and the concomitant fluctuations of pressure within the pleural space. The factors immediately responsible for the flow of air into the lungs on inspiration and for its outflow on expiration are the fluctuations of pressure within the lungs, which can be recorded if a tube connected to a manometer is introduced into a nostril, and the subject is asked to breathe with his mouth shut. Experience has shown that the pressure in the lungs drops two millimetres of mercury below atmospheric pressure on each inspiration, and rises three or four millimetres above atmospheric pressure on each expiration.

The pressure in the pleural space can be measured by puncturing the chest wall with a hollow needle connected to a manometer (Fig. 50). As soon as the needle enters the pleural space, the manometer will register a pressure below atmospheric. During quiet inspiration the intrapleural pressure is nine millimetres of mercury below atmospheric, and with quiet expiration six millimetres below. That pressure is often called *negative*, atmospheric pressure being taken as zero.

#### INTRAPLEURAL PRESSURE

The mechanism responsible for negative pressure in the chest can be demonstrated by means of a modified Donders' model.

If we place the lungs of an animal in a glass bell-jar corresponding in size to its thorax and then remove all the air from the jar by aspiration, the lungs will fill almost its entire space. At the same time the pressure in the narrow space left between the jar wall and the lungs will fall slightly below atmospheric, because the distended elastic pulmonary tissue tends to collapse. The force with which that occurs, known as the *elastic traction of lung tissue*, counteracts atmospheric pressure.

The phenomena observed in the modified Donders' model are identical with those in normal physiological conditions of inspiration and expiration. In the chest the lungs are always expanded, the expansion increasing during inspiration and decreasing with expiration, which produces negative pressure in the pleural space, rising during inspiration and falling with expiration. That the lungs are actually constantly expanded can be convincingly demonstrated by opening the chest; owing to their elastic traction the lungs immediately collapse and occupy only about one-third of the thoracic cavity.

The expansion of the pulmonary tissue depends upon the fact that atmospheric pressure acts upon the lungs only from within by way of the air passages and not from without, owing to the rigid chest wall. Therefore the lungs in the chest experience only a one-way pressure which expands them, and presses them close against the chest wall so that they fill the entire pleural cavity leaving only the narrow pleural space filled with a thin layer of serous fluid.

The force of atmospheric pressure is expended in part on overcoming the elastic traction of the lungs. Therefore the force with which the lung presses against the chest wall is less than the atmospheric pressure and, consequently, even in expiration, the intrapleural pressure is less than atmospheric by the magnitude of the elastic traction of the lungs, i. e. by about six millimetres mercury.

The elastic traction of the lungs is caused by two factors: 1) the presence of a large number of elastic fibres in the alveolar wall, and 2) the surface tension of that wall.

Neergaard showed in 1929 that about two-thirds of the elastic traction was due to the surface tension of the alveolar wall. That is in agreement with later findings that indicate that the lungs retain their elasticity even after destruction of their elastic tissue by the enzyme elastin.

Since the force of surface tension may differ in various alveoli, it might seem that some of them collapse and adhere in expiration while others remain distended. That does not occur, however, because their interior surface is covered with a thin monomolecular film of a substance insoluble in water, called *surfactant*, which has a low surface tension and prevents total collapse of the alveoli, thus regulating their size. In its absence *atelectasis* of the lungs is encountered in the newborn. Surfactant is an alpha-lecithin and is thought to be formed in the mitochondria of the epithelial cells of the alveoli. Cutting of both vagus nerves suppresses its secretion.

Recording of the intrapleural pressure in the newborn reveals that it equals atmospheric pressure during expiration and becomes negative only during inspiration.

Negative pressure in the pleural space is due to the fact that the thoracic cage grows more rapidly than the lungs in the newborn, so that the pulmonary tissue is under continuous distension (even during expiration). Another contributing factor is the high absorptive properties of the pleura, owing to which gas introduced into the pleural cavity is absorbed in a certain time and intrapleural pressure again becomes negative. Thus, there is a mechanism that actively maintains negative pressure in the pleural space.

This negative pressure is of great importance for the movement of blood along the veins. The main veins in the thoracic cavity have easily distendable walls, and the intrapleural negative pressure is therefore transmitted to them. Negative pressure in the venae

cavae is an accessory mechanism facilitating return of blood to the right heart. With an increase in negative pressure during inspiration, of course, blood flow to the heart is augmented. On the contrary, the exertion of straining or coughing can raise intrathoracic pressure to some extent so that the return of venous blood falls sharply.

#### PNEUMOTHORAX

When the thoracic cavity is opened, by injury or during operations, for example, the pressure in the pleural space becomes equal to that of the atmosphere, and the lung collapses and no longer follows the respiratory movements of the chest. What is known as open *pneumothorax* occurs. Bilateral open pneumothorax is fatal unless artificial respiration with rhythmical pumping of air into the lungs through the trachea is not applied.

If an artificial closed pneumothorax is induced in an adult by puncturing the chest wall with a syringe needle and introducing a small amount of air through it into the pleural cavity, partial collapse of the lung is caused. The lung will still take part in respiration, as in Donders' model, expanding during inspiration and collapsing on expiration, but its degree of elastic distension is diminished; in that way closure of the pathological cavities, that occur in individuals due to decomposition of pulmonary tissue and the healing of inflammatory processes are aided. The air in the pleural cavity is absorbed after a time and the lung expands. Repeated introduction of air into the pleural cavity is required to maintain the pneumothorax.

#### VOLUME OF AIR IN THE LUNGS

**Tidal volume.** At rest, man inspires and expires about 500 millilitres (300 to 600) of air, an amount known as the *tidal volume*. In addition to that volume a healthy adult may take in approximately 1,500 millilitres (*complemental volume*); similarly after a quiet inspiration he may expire about another 1,500 millilitres (*reserve or supplemental volume*). These average quantities show that quiet respiration does not involve maximum expansion or collapse of the thoracic cavity. When required, the volume of respiratory movements can be increased, both with expiration and with inspiration, so that the volume of air entering the lungs increases.

**Vital capacity of the lungs.** If, after the deepest possible inspiration, all the air is forced out of the lungs by maximum expiration into a special apparatus (*spirometer*), the tidal, reserve, and complemental volumes of air will enter it, i. e. a total, on average, of  $500 + 1,500 + 1,500 = 3,500$  millilitres. That volume is the *vital capacity of the lungs*, which varies with age, sex, health, and respiratory training. The vital capacity of the lungs in young men is

between 3.5 and 4.5 litres, in women it is about one-third less (3.0 to 3.5 litres).

**Residual air.** The deepest possible expiration does not force all the air from the lungs; something between 1,000 and 1,500 millilitres of so-called *residual air* remains in them.

Unlike the tidal, reserve, and complemental volumes, the amount of residual air cannot be measured directly, so that indirect methods have to be used. One way is as follows. The subject is asked to make a forced expiration so that only the residual air remains in his lungs. Then he takes a number of deep breaths from a gasometer and expires them back into the instrument, the capacity of which, for example three litres, is known. The gasometer is filled with a gas mixture containing 10 per cent of helium. After a number of respirations, when the composition of the air in the lungs and in the instrument has become identical, the subject is asked to make a maximum expiration. Then, by determining the concentration of helium in the instrument, the residual volume of air can be calculated as follows.

Let us assume, for example, that after the gas in the instrument has been mixed with the alveolar air the concentration of helium is found to be 7.5 per cent. As helium takes no part in the gas exchange, it spreads uniformly in the air in the instrument and in the air left in the lungs after a deep expiration. The total helium content in

the gasometer before the test was:  $\frac{3 \cdot 10}{100}$  litres; after several inspirations and expirations the total amount of helium remains the same, but it is distributed in a larger volume of air  $\frac{(3 + x) \cdot 7.5}{100}$ ,

where  $x$  is the volume of the residual air. Its value is then calculated from the two equations:  $\frac{3 \cdot 10}{100} = \frac{(3 + x) \cdot 7.5}{100}$ , so that  $x = \frac{3 \cdot 10}{7.5} - 3 = 1.0$ . Hence it follows in our example, that the volume of residual air is one litre.

The ratio of the volumes of air in the lungs is shown in Fig. 51.

With quiet respiration the lungs always contain residual and reserve air, and these volumes also remain in the lungs after death. Most of the air in the lungs of a corpse can be expelled by a bilateral open pneumothorax which produces almost complete collapse of the pulmonary tissue; the expelled air is known as *collapse air*.

Since a certain minimum amount of air remains in the lungs even after an open pneumothorax, a piece of pulmonary tissue from the lung of an adult or a newborn child which has breathed does not sink in water, but a piece of lung from a foetus, or a stillborn baby whose lungs have not been inflated, however, will sink.

**Dead space.** Air fills not only the alveoli, but also the air passages (larynx, trachea, bronchi, and bronchioles). The air in the air

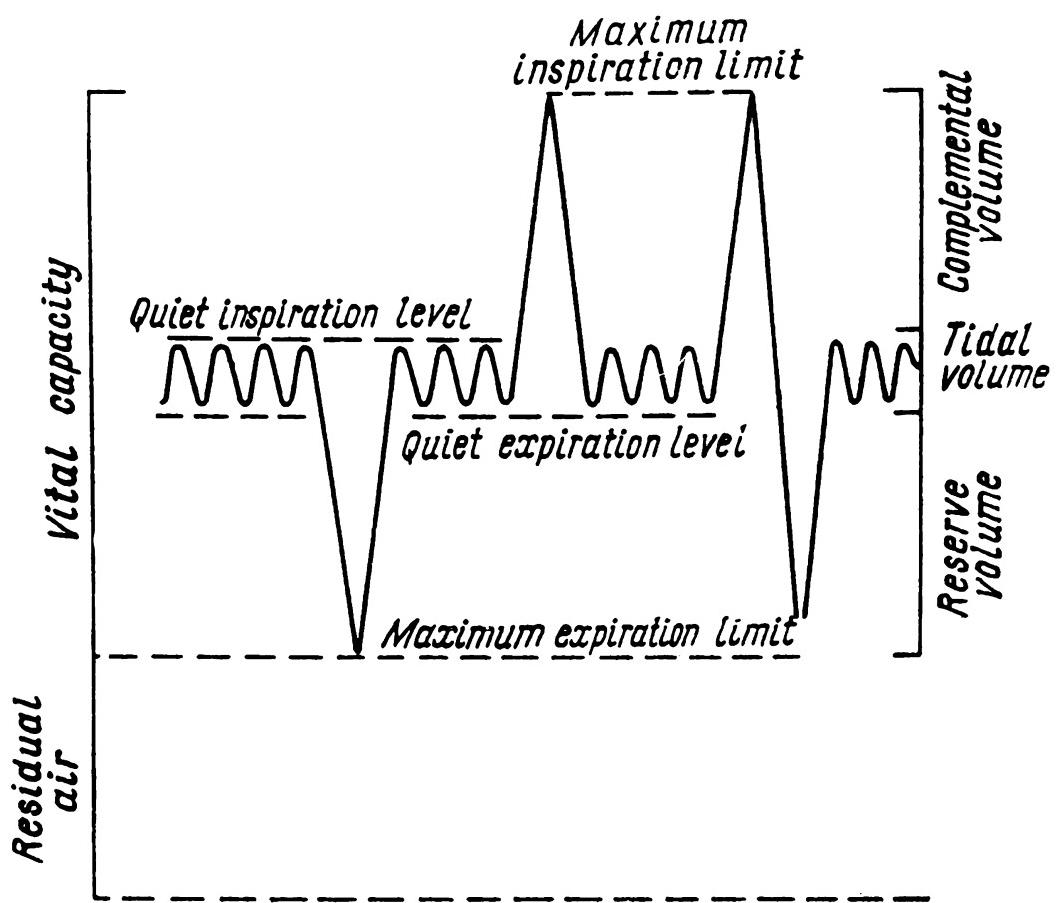


FIG. 51. Ratio of air volumes in the lungs

passages does not take part in respiratory exchange, and for that reason is known as the *dead space* air. Although its volume is light, about 140 millilitres on average, it has to be estimated in order to understand why the composition of the alveolar air differs from that expired (p. 179). Of the 500 millilitres of atmospheric air inhaled during each quiet inspiration  $500 - 140 = 360$  millilitres reach the alveoli. Since after each quiet expiration 1,000 millilitres of residual air and 1,500 millilitres of reserve air, i. e. a total of 2,500 millilitres, remain in the alveoli, all the alveolar air is not renewed at each inspiration but only  $\frac{360}{2,500}$ , i. e. about one-seventh.

#### IMPORTANCE OF THE AIR PASSAGES

While passing along the air passages, atmospheric air is cleansed of dust, warmed, and moistened.

The air is most thoroughly freed of dust when breathed through the nose. Turbulence is produced as it passes along the relatively narrow nasal passages, and the larger dust particles striking the walls of the nose, nasopharynx, and larynx, are caught by the mucous secretions covering them. The mechanism is so effective that only particles smaller than four to six microns in diameter enter the internal respiratory passages. The ciliated epithelium

of the bronchi and trachea also helps to remove dust particles.

The entry of large dust particles into the trachea and bronchi causes reflex coughing, and their presence in the nose, reflex sneezing. Both coughing and sneezing (p. 207) are respiratory defence reflexes that free the respiratory passages of foreign particles and mucus obstructing breathing.

The bronchial walls, particularly those of the smallest branches, the *bronchioles*, have a smooth circular musculature that narrows their lumen. The contraction of the muscle fibres in the terminal bronchioles can narrow the lumen to such an extent as to exclude the alveoli supplied by them from respiration because flow of air ceases.

The smooth muscles of the bronchioles are innervated by the vagus and sympathetic nerves. Stimulation of the vagus nerve causes contraction of the musculature and constriction of the bronchi, while sympathetic stimulation leads to relaxation of the muscles and dilatation of the bronchi. The contraction of the bronchial musculature on vagal stimulation can be so severe as to make respiration difficult.

#### PULMONARY VENTILATION

*The number of respiratory movements* in an adult at rest is between 16 and 20 per minute. In children the rate is greater, and in the newborn, for example is about 60 per minute.

Multiplication of the number of respirations per minute by the volume of a single inspiration, i.e. by the tidal volume, gives the *respiratory minute volume*, which averages between six and eight litres in adults.

To determine the value of pulmonary ventilation, expired air is collected for some minutes in a rubber Douglas bag through a mouthpiece or a special mask, supplied with a valve, put over the subject's face. Then the air from the bag is passed through a gasometer, the volume of expired air measured, and the minute volume of pulmonary ventilation calculated.

Minute volume is not an adequate index of the efficiency of pulmonary ventilation. That can be illustrated as follows. Let us assume that two subjects both have a minute volume of six litres. The first takes 20 breaths per minute, each of 300 millilitres, and the second ten breaths per minute, each of 600 millilitres. Taking into account that the volume of the dead space averages 140 millilitres, it is evident that about one-half of the 300-millilitre inspiratory air is spent on ventilating the dead space. Consequently, only  $300 - 140 = 160$  millilitres reach the alveoli with each inspiration. With inspirations of 600 millilitres, on the other hand,  $600 - 140 = 460$  millilitres reach the alveoli (i. e. about three-quarters of the volume). Thus, though *respiratory* the minute volume is six

litres in each case, alveolar ventilation is  $20 \times 160 = 3.2$  litres for the first subject, and  $10 \times 460 = 4.6$  litres for the second.

Thus, a less frequent but deeper respiration is much more effective since it ensures better alveolar ventilation. The example discussed shows the practical importance of respiratory exercises aimed at training correct respiration.

#### COMPOSITION OF INSPIRED, EXPIRED, AND ALVEOLAR AIR

The *atmospheric air* inhaled by man in the open air or in a well-ventilated room contains 20.94 per cent oxygen, 0.03 per cent carbon dioxide, and 79.03 per cent nitrogen. The percentage of carbon dioxide in the air of closed premises occupied by people may be somewhat higher.

*Expired air* contains 16.3 per cent oxygen, 4 per cent carbon dioxide, and 79.7 per cent nitrogen on average (the figures are given in conversion to dry air, i. e. after subtraction of the value of the water vapour content in which the expired air is always rich).

The composition of expired air is extremely variable, depending upon the intensity of metabolism and the volume of pulmonary ventilation. It changes even if a few deep breaths are taken or, on the contrary, if the breath is held.

Nitrogen does not enter into respiratory exchange, but its percentage in the expired air is fractionally above that in the inspired, since the volume of the expired air is rather less than the volume of inspired, so that the same amount of nitrogen, being distributed in a lesser volume, shows a higher percentage. Less air is expired than inspired because the amount of carbon dioxide expelled is slightly less than the amount of oxygen taken up (part of the oxygen intake is utilized by the organism in the formation of compounds excreted in the urine).

The *alveolar air* differs from that expired in its higher percentage of carbon dioxide and lower percentage of oxygen. The composition of the alveolar air averages 14.2 to 14.6 per cent oxygen, 5.5 to 5.7 per cent carbon dioxide, and about 80 per cent nitrogen.

The difference in the composition of alveolar and expired air is because the latter contains air not only from the alveoli, but also from the dead space. Air of the dead space does not differ in composition from that of the atmosphere at the end of inspiration because it does not exchange gases with the blood (Fig. 52).

To comprehend the mechanism of gas exchange in the lungs it is important to determine the composition of alveolar air, for which a simple method was suggested by Haldane. Following a normal inspiration, the subject makes the deepest possible expiration through a tube 1.0 to 1.2 metres long and 25 millimetres in diameter. The first part of the expired air expelled through the tube contains air from the dead space, while the last part in the tube

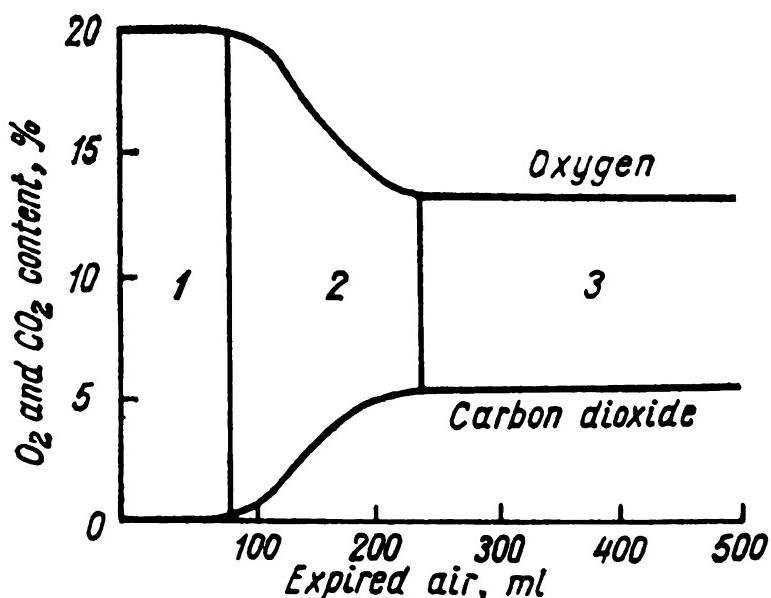


FIG. 52. Oxygen and carbon dioxide content in different portions of expired air

1 — air of dead space; 2 — air of dead space mixed with alveolar air; 3 — alveolar air

contains alveolar air. Samples of air are taken for analysis from the part of the tube closest to the mouth.

The composition of alveolar air varies somewhat, depending on whether the sample is collected at the peak of inspiration or at the peak of expiration.

If a rapid, short, and incomplete expiration is made at the end of a normal inspiration, the sample will show the composition of alveolar air encountered after inflation of the lungs with tidal air, i. e. after inspiration. But if a deep expiration is made after a normal one, the sample will show the composition of the alveolar air encountered during expiration. In the first case the percentage of carbon dioxide will clearly be slightly lower and the percentage of oxygen slightly higher than in the second. That is clear from Haldane's results; he found that the average percentage of carbon dioxide in alveolar air was 5.54 at the end of inspiration and 5.72 at the end of expiration.

Thus, there is a comparatively slight difference in the carbon dioxide content of alveolar air during inspiration and expiration, of 0.2 to 0.3 per cent, mainly because, as already mentioned, only one-seventh of the volume of the air contained in the alveoli is renewed during quiet respiration. The relative constancy of the composition of alveolar air has an essential physiological significance which will be discussed later.

#### TRANSPORT OF GASES BY THE BLOOD

The blood carries oxygen from the alveolar air to the body tissues and carbon dioxide from the body tissues to the pulmonary alveoli. Let us consider the state in which these gases occur in the blood and the factors responsible for their absorption by, and elimination from, the blood.

## ABSORPTION OF GASES BY A LIQUID

Gases may occur in a liquid either 1) as a simple *physical solution* (*absorption*), or 2) in *chemical combination*.

The amount of gas that can dissolve in a liquid is governed by a number of factors: 1) the composition of the liquid, 2) the volume and pressure of the gas above the liquid, 3) the temperature of the liquid, and 4) the nature of the gas studied. A special index has been adopted to characterize the solubility of a gas in a liquid—its *coefficient of absorption* or *solubility*. The coefficient expresses the volume of gas that will dissolve in one millilitre of liquid at 0°C with a gas pressure of 760 millimetres of mercury. The higher the pressure of the gas and the lower the temperature, the greater is the amount of gas dissolved in the liquid. With a rise in liquid temperature the solubility of gases decreases, reaching zero at boiling point. The absorption coefficient also depends upon the amount of matter dissolved in water (the more matter dissolved, the lower the absorption coefficient of gases). The solubility coefficient of oxygen in blood plasma at body temperature and a pressure of 760 millimetres of mercury is 0.022, of nitrogen 0.011, and of carbon dioxide 0.510.

## PARTIAL PRESSURE AND TENSION OF GASES

If there is a mixture of gases above a liquid, the amount of each gas dissolved in the liquid will depend directly upon the partial pressure of the gas, i. e. upon the pressure exerted by the given gas. The partial pressure of a gas in a mixture can be calculated if the total pressure and the percentage composition of the mixture are known. At an atmospheric pressure of 760 millimetres of mercury, for example, the partial pressure of the oxygen in air is approximately 21 per cent of 760 millimetres, or 159 millimetres, and of nitrogen 79 per cent of 760 millimetres, or 601 millimetres. It should be borne in mind, when calculating the partial pressure of gases in alveolar air, that the latter is saturated with water vapours, the partial pressure of which at body temperature is 47 millimetres of mercury. For that reason, the total 760 millimetres do not fall to the share of the other gases (nitrogen, oxygen, and carbon dioxide) but only  $760 - 47 = 713$  millimetres. With a 14.3 per cent content of oxygen in the alveolar air, its partial pressure will be only 102 millimetres; with 5.6 per cent of carbon dioxide, the partial pressure of that gas will be 40 millimetres.

If a liquid saturated with a gas at a definite partial pressure comes in contact with that same gas at a lower pressure, some of the gas will escape from the solution and the amount of dissolved gas will be reduced. When the pressure of the gas is higher, however, more gas will dissolve in the liquid.

The solubility of gases is governed by their partial pressure, i. e. by the pressure of the given gas, and not by the total pressure of the gaseous mixture, which is why oxygen dissolved in a liquid, for example, will escape into a nitrogen atmosphere, as it does into a vacuum, even though the nitrogen is under very high pressure.

The amount of gas entering or leaving a liquid on contact with a definite mixture of gases depends not only upon the pressure of that gas in the liquid and in the mixture, but also upon the volume of the liquid and of the gas mixture. Large amounts of gas can enter or leave a liquid if a large volume of liquid comes into contact with a large volume of a gas mixture, that differs sharply in pressure from the gases in the liquid. On the contrary, on contact of a small bubble of gas with quite a large volume of liquid, only a slight amount of gas will leave the liquid or enter it, and the gas content of the liquid will not in practice be changed.

The term "*tension*" is applied to gases dissolved in a liquid, and corresponds to the term "partial pressure" used in reference to free gases. *Tension* is expressed in the same units as pressure, i. e. in atmospheres or in millimetres of mercury or water. A gas tension of 100 millimetres of mercury means that the gas dissolved in a liquid is in equilibrium with a free gas with a pressure of 100 millimetres.

The equilibrium is disturbed if the tension of the gas dissolved is not equal to the partial pressure of the free gas. It is restored when these two values are equalized. For example, if the tension of oxygen in a liquid contained in a closed vessel is 100 millimetres, and the pressure of oxygen in the air in the vessel is 150 millimetres, oxygen will enter the liquid. The tension of the gas in the liquid will rise, while its pressure outside will fall, until a new dynamic equilibrium is reached, and both indices become equal at a new value somewhere between 100 and 150 millimetres. The character of the changes in pressure and tension in any given case will depend upon the relative volumes of the gas and liquid.

#### THE GAS CONTENT OF BLOOD

Calculations indicate that 100 millilitres of arterial blood should contain 0.3 volume per cent of dissolved oxygen, 2.5 volume per cent carbon dioxide, and 0.95 volume per cent nitrogen, but much more oxygen and carbon dioxide can be derived from blood using methods described below, which shows that these gases occur in the blood not only in a state of physical solution but also chemically combined. Oxygen is combined with haemoglobin; carbon dioxide is partially combined with haemoglobin, but occurs mainly in the form of bicarbonate.

**Extraction of gases from blood.** Complete extraction of gases from the blood was first performed in 1859 by Sechenov who devised

a mercury pump for the purpose based on the principle of restored vacuum.

A sample of blood collected directly from a blood vessel is put into the receiver of Sechenov's apparatus, which is cut off from a glass cylinder by a tap. A vacuum is produced in the cylinder by means of a mercury pump, and then the cylinder is connected with the receiver containing the blood by turning the tap. Gases begin to escape from the blood immediately, as if it were boiling. The escape of gases soon ceases as equilibrium is established between those remaining in the blood and those in the cylinder. Then the tap is turned off, and the gases are driven from the cylinder into a measuring vessel by means of the same mercury pump. A vacuum is again produced in the cylinder, and the tap connecting it with the blood receiver is again turned on. A new portion of gases escapes from the blood until a new equilibrium is established. By repeating the procedure several times, practically all the gases in the blood can be extracted.

Apparatus using the principle of driving off gases from the blood by chemical action are also employed. *Barcroft's apparatus* is the most used; it measures the amount of oxygen withdrawn from the blood through the addition of potassium ferricyanide, and the amount of carbon dioxide released by the addition of tartaric acid.

*Van Slyke's apparatus*, which combines the principles of Sechenov's and Barcroft's devices, is widely used. It involves both the driving off gases by chemical compounds and their extraction by means of vacuum produced with a mercury pump.

**The oxygen capacity of blood.** As well as finding the oxygen content of blood, its *oxygen capacity*, or the maximum amount of oxygen that can be absorbed by 100 millilitres of blood, is determined. For that purpose blood drawn from a blood vessel is brought in contact with air so that it becomes fully saturated with oxygen.

The oxygen capacity of the blood depends upon its haemoglobin content. Each gramme of haemoglobin can take up 1.34 millilitres oxygen. With a 14 per cent haemoglobin content, 100 millilitres of blood can take up  $14 \times 1.34$ , or 19 millilitres of oxygen. That value (19 volumes per cent) is the normal oxygen capacity of blood. Knowing the oxygen capacity and oxygen content of blood drawn from a blood vessel and not exposed to air, we can calculate its *percentage oxygen saturation*, or the ratio between the oxygen content of the blood examined and its oxygen capacity.

To determine the gas content of the blood in a blood vessel, a sample is taken from it with a syringe and ejected under a layer of vaseline oil or ammonia so that it does not come into contact with the air and thus retains its initial amount of gases.

**The gas content of arterial and venous blood.** The arterial blood of a healthy person contains 18 to 20 volumes per cent of oxygen,

50 to 52 volumes per cent of carbon dioxide, and about one volume per cent of nitrogen. The corresponding values for venous blood are 12 volumes per cent, 55 to 57 volumes per cent, and approximately one volume per cent which indicate that venous blood, while flowing along the lung capillaries, becomes richer in oxygen and gives off some of its carbon dioxide. Arterial blood, on entering the capillaries of the systemic circulation, loses some of its oxygen and becomes saturated with carbon dioxide. The identical nitrogen content of arterial and venous blood indicates that it does not take part in the interchange of gases.

#### TRANSPORT OF OXYGEN BY THE BLOOD

Most of the oxygen is carried by the erythrocytes. Only 0.3 volume per cent of the total 19 volumes per cent of oxygen extracted from arterial blood is dissolved in the plasma; the remainder is contained in the erythrocytes in the form of an unstable, easily dissociable chemical combination with *haemoglobin* (Hb) known as *oxyhaemoglobin* ( $\text{HbO}_2$ ). The binding of oxygen by haemoglobin is governed by the oxygen tension and is readily reversible. With a fall in oxygen tension, oxyhaemoglobin gives up oxygen.

**Oxyhaemoglobin dissociation curves** are constructed by plotting the partial pressures of oxygen on the abscissa and the percentage oxygen saturation of haemoglobin, i. e. the percentage of haemoglobin converted to oxyhaemoglobin, on the ordinate. The curve (Fig. 53) resembles a hyperbola in shape and shows that there is no direct ratio between the partial pressure of oxygen and the amount of oxyhaemoglobin formed. The left part of the curve rises steeply, while the right part runs almost horizontally. The curve has physiological significance. Changes in oxygen partial pressure within the zone of relatively high values, i. e. between 100 and 60 millimetres mercury, which corresponds to the pressure of oxygen in the alveoli, have no marked influence upon the horizontal part of the curve, that is to say, cause almost no changes in the amount of oxyhaemoglobin formed.

Curve A in Fig. 53 was obtained from analysis of a solution of pure haemoglobin in distilled water. In natural circumstances, however, blood plasma contains various salts and carbon dioxide which alter the oxyhaemoglobin dissociation curve slightly. The left-hand part is deflected so that the entire curve becomes S-shaped. In curve B the middle part falls steeply while the lower part tends to the horizontal. It should be noted that the lower part of the curve characterizes the properties of haemoglobin in a zone of low partial pressures of oxygen with values close to those encountered in tissues. The middle part of the curve indicates the properties of haemoglobin at oxygen tension values similar to those in arterial and venous blood.

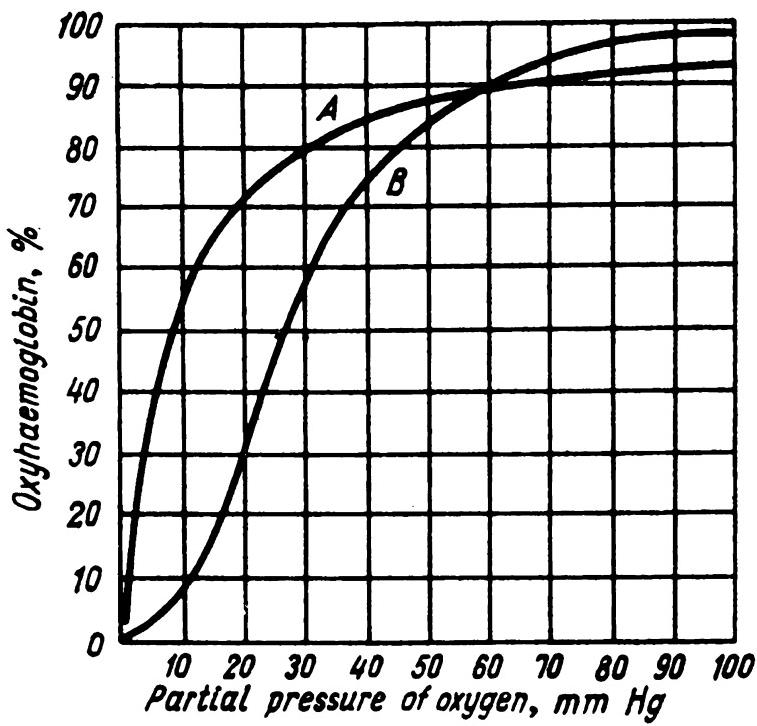


FIG. 53. Oxyhaemoglobin dissociation in distilled water solution (A) and in blood (B) at carbon dioxide tension of 40 millimetres mercury (after Barcroft)

**Changes in oxyhaemoglobin dissociation in relation to concentration of hydrogen ions and temperature.** With an increase in the concentration of hydrogen ions in the blood, i. e. with a fall in pH, the affinity of haemoglobin for oxygen diminishes. Therefore less oxyhaemoglobin is formed with an increase in carbon dioxide tension, oxygen partial pressure remaining constant (Fig. 54), a phenomenon first noticed by Werigo, and analysed in detail by Bohr.

A sharp reduction in the oxygen-absorption ability of haemoglobin occurs in the presence of carbon dioxide at an oxygen pressure of 40 millimetres of mercury, i. e. at the pressure encountered

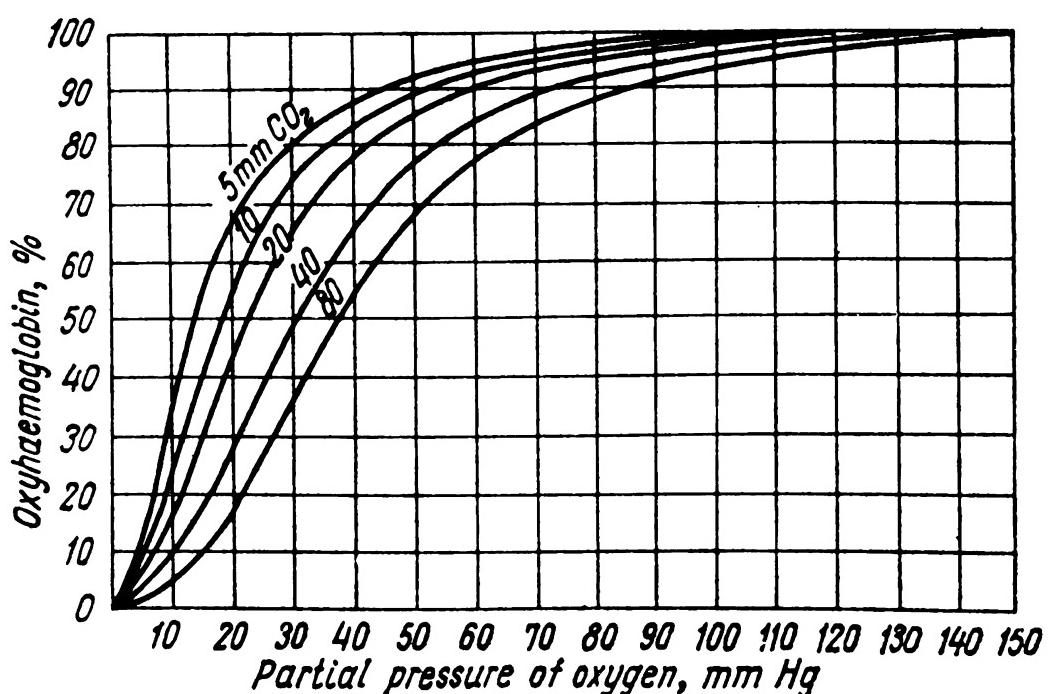


FIG. 54. Variation of oxyhaemoglobin dissociation curves with changes in the tension of carbon dioxide

in the venous blood. This property of haemoglobin is of great importance to the organism. The tension of carbon dioxide in the blood flowing in tissue capillaries increases, and as a result the ability of haemoglobin to combine with oxygen falls and more oxygen is given off to the tissues. In the alveoli of the lungs, some carbon dioxide escapes into the alveolar air, the affinity of haemoglobin for oxygen increases, and the formation of oxyhaemoglobin is thus facilitated.

A particular marked decrease in the oxygen-binding properties of haemoglobin is encountered in the blood of muscle capillaries during strenuous muscular exertion, when acid metabolites, lactic acid in particular, invade the blood, which facilitates the release of a large amount of oxygen into the muscles.

The ability of haemoglobin to combine with or give off oxygen also varies with temperature. With the same partial pressure of oxygen in the surrounding medium, oxyhaemoglobin gives up more oxygen at human body temperature ( $37^{\circ}$  to  $38^{\circ}\text{C}$ ) than it does at lower temperatures.

#### TRANSPORT OF CARBON DIOXIDE

Venous blood may yield 55 to 58 volumes per cent of carbon dioxide, most of which comes from carbonates present in the plasma and erythrocytes. Only about 2.5 volumes per cent is in a solution, while 4 or 5 volumes per cent are bound with haemoglobin in the form of *carbohaemoglobin*.

The formation of carbonic acid from carbon dioxide takes place in the erythrocytes, which contain an enzyme known as carbonic anhydrase, a powerful catalyst that accelerates the  $\text{CO}_2$  hydration reaction.

**Carbonic anhydrase.** The existence of this enzyme was assumed by Sechenov, but it was only discovered in 1932 by Meldrum and Roughton.

The presence of carbonic anhydrase has been revealed not only in the erythrocytes, but also in the pancreas, salivary glands, gastric mucosa, kidneys, central nervous system, and retina. The enzyme is concerned with the formation of hydrochloric acid in the stomach, and bicarbonates in the pancreatic juice and saliva. Its activity depends upon the condition of the body, increasing during oxygen deficiency and breathing in evacuated space, and suffering changes during various diseases.

Carbonic anhydrase accelerates the reaction



in either direction, depending upon the tension of carbon dioxide, in other words, it is capable of catalysing the reaction either in the direction of hydration or in the direction of dehydration.

Thus, in the tissue capillaries, where carbon dioxide tension is high, carbonic acid is produced from  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . But in the blood flowing through the lungs and marked by a lower tension of carbon dioxide carbonic anhydrase increases the speed of the dehydration reaction, as a result of which carbon dioxide is eliminated from the blood.

**Binding of carbon dioxide in the capillaries of the systemic circulation.** Carbon dioxide produced in the tissues diffuses into the blood of the capillaries since its tension in the tissues is much greater than in the arterial blood. Being soluble in plasma, carbon dioxide diffuses into the erythrocyte where it is immediately converted to carbonic acid under the effect of carbonic anhydrase. It has been calculated that the activity of the enzyme in the erythrocyte is such that carbon dioxide hydration is accelerated 1,500 to 2,000 times. Since all carbon dioxide in the erythrocyte is converted to carbonic acid, the  $\text{CO}_2$  tension within the blood corpuscle drops to nearly zero and new amounts of the gas enter the erythrocyte. The formation of carbonic acid leads to an increase of  $\text{HCO}_3^-$  ion concentration within the erythrocyte, and these ions begin to diffuse into the plasma, which is possible as the cell-membrane of the erythrocyte is permeable to anions, but practically impermeable to cations. An ion of chloride enters the erythrocyte in exchange for the  $\text{HCO}_3^-$  ion. The diffusion of chloride ions from the plasma into the erythrocyte results in the release of sodium ions in the plasma, which combine with the  $\text{HCO}_3^-$  ions diffusing from the erythrocyte to form  $\text{NaHCO}_3$ . Chemical analysis of venous plasma shows a marked increase in its bicarbonate content.

The accumulation of anions inside the erythrocyte leads to an increase in its osmotic pressure which causes the passage of water from the plasma through the erythrocyte membrane. As a result, the erythrocytes in the capillaries of the systemic circulation increase in volume. Haematocrit studies have shown that the erythrocytes account for 40 per cent of the arterial blood volume and for 40.4 per cent of the venous blood volume, which means that the volume of erythrocytes in venous blood is greater than in the arterial blood, and that is due to their uptake of water from venous blood.

Simultaneously with the diffusion of  $\text{CO}_2$  into the erythrocyte and the formation of carbonic acid there oxygen is liberated by oxyhaemoglobin and converted into reduced haemoglobin, which is a considerably less dissociable acid than either oxyhaemoglobin or carbonic acid. Because of that,  $\text{H}_2\text{CO}_3$  displaces potassium ions from haemoglobin on the reduction of oxyhaemoglobin, and combines with them to form potassium bicarbonate salt.

The  $\text{H}_3^+$  ion liberated from the carbonic acid combines with the haemoglobin, and since reduced haemoglobin is a weakly dissociable acid, the acidity of the blood does not rise, so that the pH difference between arterial and venous blood is negligible. The reaction occur-

ring in erythrocytes in the tissue capillaries can be expressed as follows:

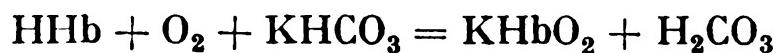


It is obvious from the data presented above that oxyhaemoglobin, on being converted to haemoglobin and giving up the bases connected with it to carbon dioxide, facilitates the production of bicarbonate and the transport of carbon dioxide in that form.

In addition, haemoglobin forms a chemical compound with CO<sub>2</sub>, known as *carbohaemoglobin*. The presence of this combination of haemoglobin with carbon dioxide in blood was revealed by the following experiment. After potassium cyanide, which completely inactivates carbonic anhydrase, had been added to whole blood the erythrocytes combined with a larger amount of CO<sub>2</sub> than did the plasma. That led to the conclusion that the binding of CO<sub>2</sub> by the erythrocytes, following the inactivation of carbonic anhydrase, is accounted for by the existence of a haemoglobin-CO<sub>2</sub> compound in them. Later it was found that the CO<sub>2</sub> combines with the amino group of haemoglobin, forming the so-called *carbamino compound*.

The reaction can take place in either direction, depending upon the carbon dioxide tension in the blood. Although only a small proportion of the total amount of carbon dioxide extracted from the blood is combined with haemoglobin (8 to 10 per cent), the compound plays quite an important role in the transport of carbon dioxide by the blood. About 25 to 30 per cent of carbon dioxide absorbed by the blood in the systemic capillaries is thus bound by haemoglobin to form carbohaemoglobin.

**Release of carbon dioxide in the lung capillaries.** Since its partial pressure in alveolar air is lower than its tension in venous blood, carbon dioxide diffuses from the blood of the lung capillaries into the alveolar air, and its tension in the blood drops. Simultaneously, oxygen passes from the alveolar air into the blood since its partial pressure in the air is higher than its tension in the blood. Therefore the tension of oxygen in the blood rises and haemoglobin is converted into oxyhaemoglobin. As the latter is an acid that dissociates more readily than either haemoglobin or carbonic acid, it displaces carbonic acid in the potassium bicarbonate salt, the following reaction taking place:



The carbonic acid freed from combination with bases is split by carbonic anhydrase into carbon dioxide and water. The importance of carbonic anhydrase in the elimination of carbon dioxide in the lungs is demonstrated by the following data. It takes 300 seconds to dehydrate enough H<sub>2</sub>CO<sub>3</sub> dissolved in water to produce the amount of carbon dioxide that diffuses out of the blood while

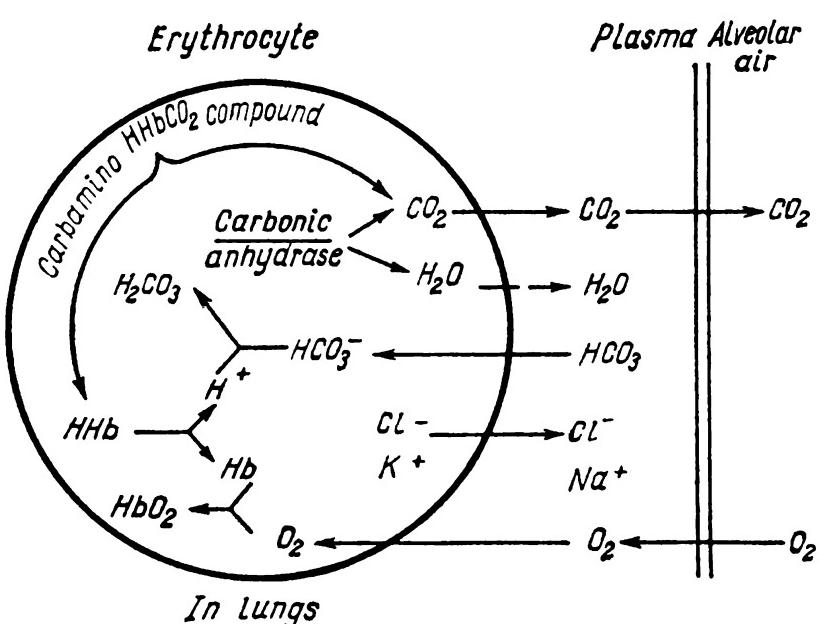
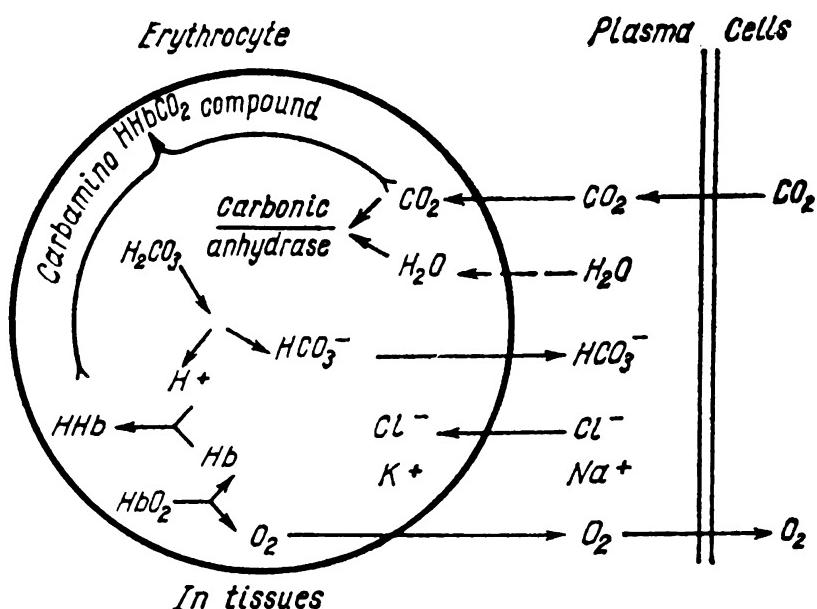


FIG. 55. Schematic representation of processes occurring in an erythrocyte during absorption or release of oxygen and carbon dioxide by the blood

it flows along the lung capillaries. But in the one or two seconds that it takes blood to pass along the capillaries the carbonic acid in the erythrocyte is dehydrated and the liberated  $CO_2$  diffuses first into the blood plasma and then into the alveolar air.

Since the concentration of  $HCO_3^-$  ions in the erythrocytes of the pulmonary capillaries decreases, there is diffusion of these ions from the plasma into the erythrocytes, while  $Cl^-$  ions diffuse from the erythrocytes into the plasma; and because of the decline in carbon dioxide tension in the blood of the capillaries, the carbamino compound breaks and carbohaemoglobin gives off carbon dioxide.

All these processes are presented schematically in Fig. 55.

**Dissociation curves of carbon dioxide.** As has already been mentioned, more than 85 per cent of the carbon dioxide extract-

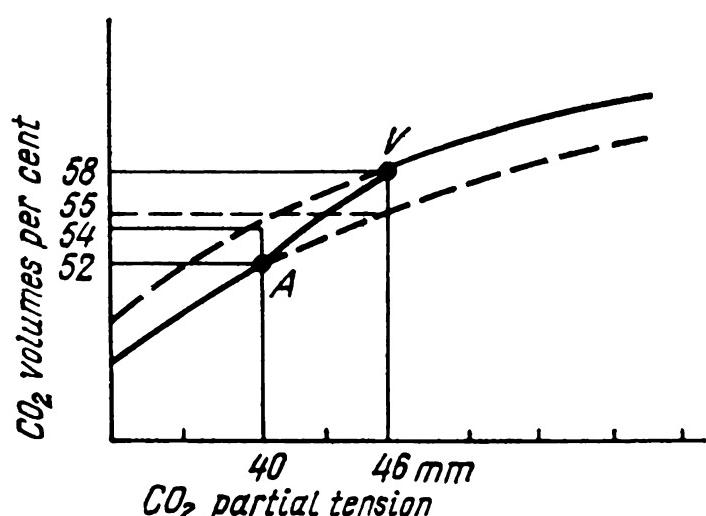


FIG. 56. Carbon dioxide dissociation curves of blood (discussed in the text)

ed from blood through acidification is released as the result of the breakdown of bicarbonates (potassium in the erythrocytes and sodium in the plasma).

The uptake and release of carbon dioxide by the blood is governed by its partial pressure. Carbon dioxide dissociation curves similar to those for oxyhaemoglobin dissociation curves can be constructed by plotting the values in volumes per cent of carbon dioxide absorbed by the blood along the ordinate and the values of carbon dioxide tension along the abscissa. The lower curve in Fig. 56 shows the uptake of carbon dioxide by arterial blood with haemoglobin almost fully saturated with oxygen. The upper curve shows the uptake of carbon dioxide by venous blood. The difference in the heights of these curves is accounted for by the fact that the arterial blood, rich in oxyhaemoglobin, is less capable than venous blood of binding carbon dioxide. Being a stronger acid than carbonic acid, oxyhaemoglobin combines with the bases in the bicarbonates and so facilitates the liberation of carbonic acid. On conversion into haemoglobin in the tissues, oxyhaemoglobin gives up the bases, so contributing to the uptake of carbon dioxide by the blood.

Point A on the lower curve in Fig. 56 corresponds to a carbon dioxide tension of 40 millimetres of mercury, i. e. to the tension actually encountered in arterial blood. With this tension carbon dioxide absorption reaches 52 volumes per cent. Point V on the upper curve represents a carbon dioxide tension of 46 millimetres of mercury, i. e. the tension actually encountered in venous blood. As will be seen from the curve, venous blood absorbs 58 volumes per cent of carbon dioxide at that tension. The line AV connecting the upper and lower curves represents the changes in carbon dioxide absorption that occur with the conversion of arterial blood into venous, or venous into arterial.

Venous blood gives off about 6 volumes per cent of CO<sub>2</sub> in the pulmonary capillaries through conversion of haemoglobin into oxyhaemoglobin. If that conversion did not take place in the lungs,

then, as can be seen from the curve, with a pressure of carbon dioxide of 40 millimetres in the alveoli venous blood would hold 54 volumes per cent of carbon dioxide, losing consequently not 6 but only 4 volumes per cent. Similarly, arterial blood flowing in the systemic capillaries would not release oxygen, i. e. its haemoglobin would remain saturated with oxygen, and at the carbon dioxide pressure encountered in the tissue capillaries would absorb not 58 but only 55 volumes per cent carbon dioxide.

Thus, the conversion of haemoglobin into oxyhaemoglobin in the lungs and the conversion of oxyhaemoglobin into haemoglobin in the body tissues are responsible for the absorption and liberation of about 3 or 4 of the total 6 volumes per cent of carbon dioxide absorbed by the blood in the tissues and given off in the lungs. About 25 to 30 per cent of the carbon dioxide liberated in the lungs is carried by carbohaemoglobin.

From what has been said above, it follows that the erythrocytes, which contain haemoglobin and carbonic anhydrase, have an essential role in the transport of both oxygen and carbon dioxide by the blood.

## GAS EXCHANGE IN LUNGS AND TISSUES

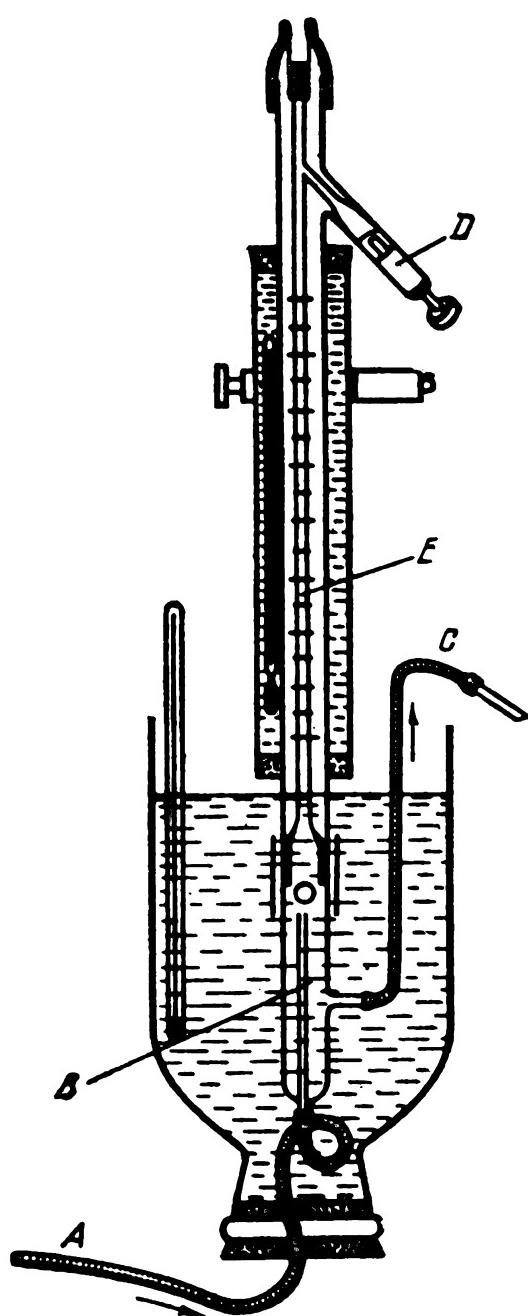
### GAS EXCHANGE IN THE LUNGS

The carbon dioxide tension in the venous blood entering the lungs is higher, and the oxygen tension lower than the pressures of these gases in the alveolar air. Therefore, blood gives off carbon dioxide and absorbs oxygen while flowing through the lung capillaries. The exchange of gases between blood and alveolar air is facilitated by the vast number of alveoli (reaching 750 million in man), and by their large surface which is 100 square metres during inspiration and 30 square metres during expiration. The membrane separating the blood from the alveolar air is only 0.004 of a millimetre thick and consists of two layers of cells, those of the capillary endothelium and those of the alveolar epithelium, which permit free passage of gases.

Gas exchange occurs as a result of diffusion of carbon dioxide from the blood into the alveolar air and diffusion of oxygen from the alveolar air into the blood, a diffusion that takes place because of the difference between their partial pressures in the alveolar air and their tension in the blood, proof of which has been obtained by measurement.

The tension of gases in the blood is measured by means of *Krogh's microtonometer* (Fig. 57). This device is inserted between the peripheral and central ends of a divided blood vessel, either artery or vein. Blood from the vessel flows along tube A into an ampule B containing a small bubble of air, and then returns through tube C to the vessel (Fig. 57).

FIG. 57. Krogh's microtonometer (discussed in the text)



Since the volume of the air bubble is negligible in comparison with the mass of flowing blood, the amount of gases that passes into it from the blood until equilibrium is established is very small and the tension of the gases in the blood does not change. The bubble is drawn from time to time into a capillary tube *E* by means of a screw *D*, and its volume measured; as soon as dynamic equilibrium is reached and the volume of the bubble becomes constant, the bubble is drawn out and its gas content is determined. The partial pressures of the gases are calculated from their percentage ratios. Since the gases in the bubble and the blood are in equilibrium, the gas tensions in the blood clearly can be calculated once the gas content of the bubble has been determined.

It has been established that the tension of oxygen in arterial blood is 100 millimetres of mercury, and of carbon dioxide 40 millimetres; the oxygen tension of venous blood is

40 millimetres and the carbon dioxide tension 46 millimetres.

These values show that the difference between the tension of the gases in venous blood and their pressure in alveolar air is about  $110 - 40 = 70$  millimetres for oxygen and  $46 - 40 = 6$  millimetres of mercury for carbon dioxide.

The tension of the gases in the blood becomes almost identical with their partial pressure in the alveolar air within the short interval that the blood is in the lung capillaries, which can be seen from the fact that the carbon dioxide tension in arterial blood is almost the same as that in alveolar air, while the oxygen tension is between two and ten millimetres less.

Experiments have shown that, with a pressure difference of only one millimetre of mercury, between 25 and 60 millimetres of oxygen may pass into the blood of a healthy adult at rest per minute. Since a resting individual requires 250 to 300 millilitres of oxygen per minute on average, a 70 millilitre pressure difference is amply

sufficient for an adequate supply of oxygen to the blood, and will meet the requirements for considerably more oxygen during physical work or sport for example, when the minute volume of blood ejected by the heart increases sharply and it flows through the lungs at a higher rate.

Because carbon dioxide diffuses from the blood twenty-five times more rapidly than oxygen, it is also able to escape in sufficient amount because of the difference between its tension in the blood and its pressure in the alveolar air.

**Ventilation and circulation in separate parts of the lungs.** Haldane drew attention to the fact that ventilation differs in various parts of the lung.

It is known that the external zone of pulmonary tissue down to 25 or 30 millimetres is the most expandable; the intermediate zone, which surrounds the branchings of the bronchi and blood vessels, is less expandable. The inner zone, lying at the root of the lung close to the main bronchi, the large blood vessels, and the connective tissue, is the least expandable. In a resting man it is the most expandable outer zone of the pulmonary tissue that is mainly involved in respiration.

The inequality in ventilation of the various parts of the lung has been demonstrated experimentally by Fowler by means of a *nitrometer* that allowed continuous automatic recording of the nitrogen concentration in expired air.

The working principle of the nitrometer is the property of the gas to glow in a high voltage field. The concentration of nitrogen is determined by drawing a small portion of expired air through a gas-discharge tube. The high voltage (2,000 volts) supplied to the tube creates luminescence in the gas. A light filter ensures that only light rays of the wave length characteristic of nitrogen fall on a photocell. Changes in the photocell are registered by a galvanometer, and the instrument is sensitive to changes occurring within 0.05 of a second.

In Fowler's experiments the subject inhaled deeply from a gasometer containing pure oxygen and exhaled evenly and slowly into a tube from which some of the expired air was drawn continuously through the nitrometer (Fig. 58). The first portion of expired air at the beginning of expiration came from the dead space and contained pure oxygen. The following portions contained gradually increasing amounts of nitrogen that had remained in the alveoli and mixed with oxygen. Pure alveolar air containing a mixture of oxygen and nitrogen was expelled at the peak of expiration. If all alveoli were ventilated identically, oxygen would be equally distributed in them and the concentration of nitrogen in the expired alveolar air would be constant over the second half of the expiration. In fact, the nitrogen concentration increased throughout the entire expiration, which was attributed to the well-ventilated alveoli,

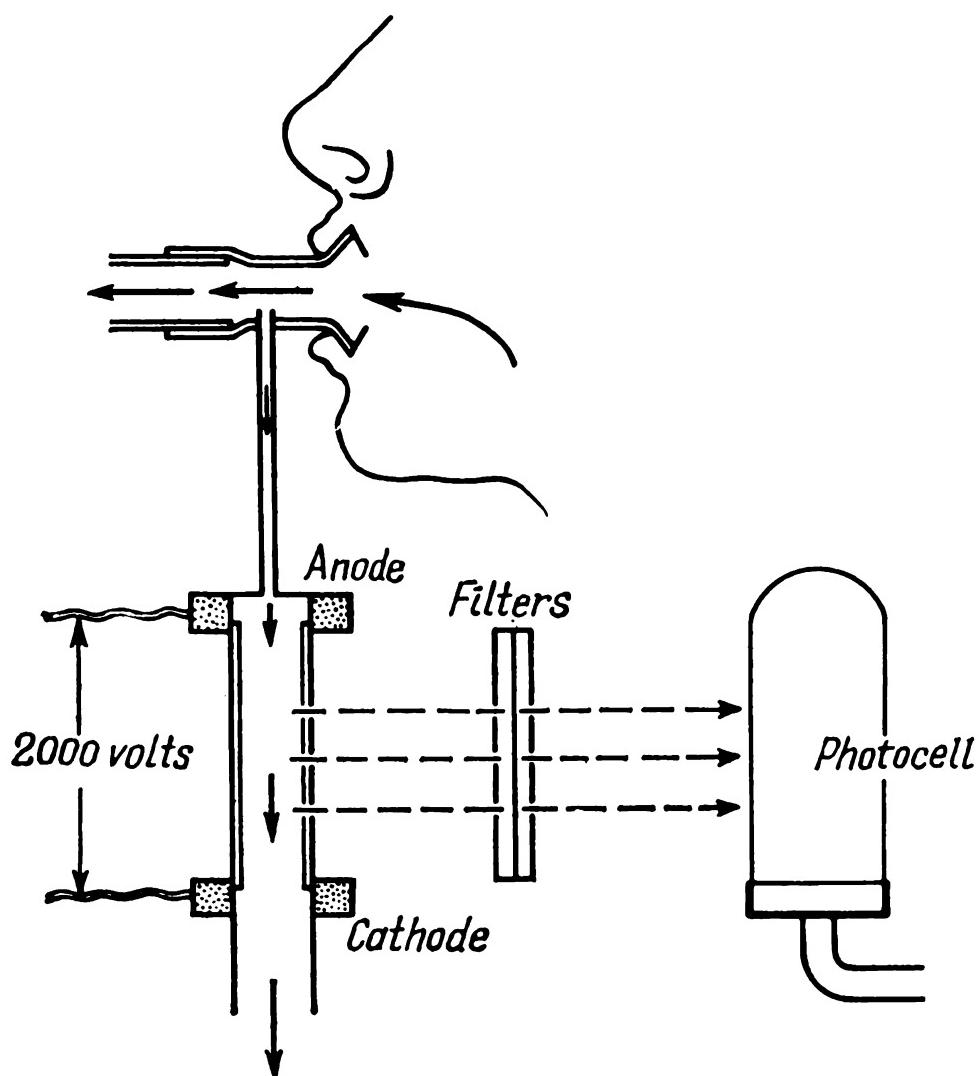


FIG. 58. Nitrometer

which expanded more easily in aspiration and from which air was first expelled in expiration, being richer in oxygen than the poorly-ventilated ones, which expanded less and which gave off their air later and in a smaller volume.

Blood supply also differs in the various parts of the lungs, the bulk flowing through the functioning alveoli; passage of blood through those parts of the lungs that are not ventilated is sharply reduced. As a result, the blood flowing in the pulmonary capillaries is almost completely arterialized. (If the non-ventilated alveoli were supplied as adequately as the well-ventilated ones, the blood flowing from the lungs would be undersaturated with oxygen.)

Agreement between blood flow and the volume of ventilation in different parts of the lungs is maintained by control mechanisms that arrest its passage through non-ventilated areas. In fact it has been established that the extent of the blood supply is controlled by the oxygen content of the alveoli, as follows from the experiments conducted by Dirken and Heemstra on separate ventilation of the right and left lungs with gas mixtures differing in their oxygen con-

tent. Blood flow fell in the lung ventilated with a mixture poor in oxygen, and increased considerably in the one ventilated with a mixture with a high oxygen content. Reduction of the partial pressure of oxygen in alveolar air apparently leads to constriction of the pulmonary arterioles.

The mechanisms by which the circulation in separate parts of the lungs is brought into conformity with their ventilation are still not sufficiently known. It has been found that acetylcholine injected into the pulmonary artery causes dilatation of the pulmonary arterioles, including those in the non-ventilated parts; blood begins to flow through the non-ventilated areas and arterialization is impaired.

The control of this relationship between the ventilation and circulation in various alveoli persists in isolated lungs which gives grounds for assuming that it is effected by way of a nervous system located within the organ itself of the type of the so-called peripheral axon reflex (See Vol. II, Chapter 16, Axon Reflexes).

#### GAS EXCHANGE IN THE TISSUES

In the tissues blood gives up oxygen and absorbs carbon dioxide. In systemic tissue capillaries the exchange occurs by diffusion, as in the pulmonary capillaries, owing to the difference in partial pressure of the gases in the blood and in the tissues.

The tension of carbon dioxide may be as high as 60 millimetres in cells; in the tissue fluid its level is extremely variable, averaging 46 millimetres, and in the arterial blood supplied to the tissues it is 40 millimetres. Passing by diffusion in the direction of lower tension, carbon dioxide escapes from the cells first into the tissue fluid and then into the blood, changing it into venous, so that its tension in the blood in the capillaries becomes identical with its tension in the tissue fluid.

Cells utilize oxygen extremely actively; consequently, its partial tension in cell protoplasm is very low, and may fall to zero with intensification of cell activity. The tension of oxygen in tissue fluid varies between 20 and 40 millimetres, so that the gas passes continuously into the tissue fluid from the arterial blood in the systemic capillaries (where its tension reaches 100 millimetres mercury). As a result, the oxygen tension in the venous blood flowing from tissues is much lower than in the arterial blood and is around 40 millimetres.

While flowing through the systemic capillaries, blood does not give up all its oxygen. Arterial blood contains about 20 volumes per cent of oxygen, and venous blood approximately 12 volumes per cent. Thus, the tissues receive 8 volumes per cent from the total of 20, i. e. 40 per cent of all the oxygen in the blood.

The amount of oxygen received by the tissues, expressed as a percentage of the total oxygen content of arterial blood is known as the *coefficient of oxygen utilization*. It is calculated by finding the oxygen content difference of arterial and venous blood, dividing that by the oxygen content of the arterial blood and multiplying the result by 100.

The coefficient of oxygen utilization varies with certain physiological conditions, but is between 30 and 40 per cent in a resting body. The oxygen content in venous blood coming from a strenuously working muscle drops to 8 to 10 volumes per cent, and oxygen utilization consequently rises to 50 or 60 per cent.

The opening of non-functioning capillaries in a working tissue facilitates more rapid passage of oxygen into it. The coefficient of utilization increases also with intensification of formation of lactic and carbonic acids since that reduces the affinity of haemoglobin for oxygen and leads to more rapid diffusion of the gas from the blood. Finally, a rise in the temperature of working muscle, and intensification of fermentation and energy-producing processes in the cells, also increase oxygen utilization. Thus, the oxygen supply to the tissues is controlled according to the intensity of the oxidation processes.

## CONTROL OF RESPIRATION

### RESPIRATORY CENTRE

*Respiratory centre* is the term applied to groups of nerve cells located in various parts of the central nervous system, that are responsible for the co-ordinated rhythmical activity of the respiratory muscles, and for the adaptation of respiration to the changes occurring in the internal and external media of the organism.

Certain groups of nerve cells, located in the reticular formation of the medulla oblongata are indispensable to the rhythmical activity of the respiratory muscles, and form the respiratory centre proper. Any impairment of their function results in respiratory arrest through paralysis of the respiratory muscles.

**Innervation of the respiratory muscles.** The medullary respiratory centre sends impulses to motoneurones in the anterior horns of the grey matter of the spinal cord concerned with innervation of the respiratory musculature.

The motoneurones whose processes form the phrenic nerves innervating the diaphragm are located in the anterior horns of the third and fourth cervical segments; those whose processes form the intercostal nerves supplied to the intercostal muscles lie in the anterior horns of the thoracic portion of the spinal cord. Hence it is clear that section of the spinal cord between the thoracic and cervical segments will stop costal respiration, but diaphragmatic respiration will persist because the motor nucleus of the phrenic nerve located

above the section retains its connection with the respiratory centre and the diaphragm. Section of the spinal cord below the medulla causes complete respiratory arrest and death due to asphyxia. After such a section, however, the auxiliary respiratory muscles of the nostrils and larynx which are innervated by nerves arising directly from the medulla itself continue to contract for some time.

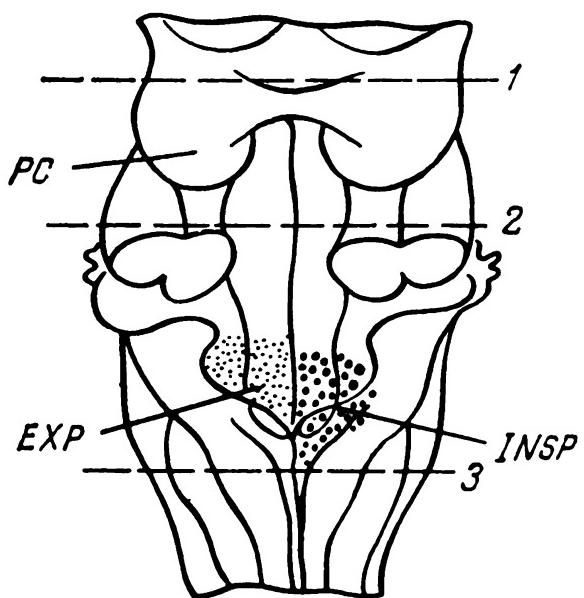
**Localization of the respiratory centre.** It was already known in antiquity that injury to the spinal cord below the level of the medulla oblongata caused death. This fact was explained in 1812 by Legallois, who cut the spinal cord in birds, and in 1842 by Flourens who stimulated and destroyed medullary areas. These authors provided experimental evidence that the respiratory centre is localized in the medulla oblongata. Flourens assumed the respiratory centre to be a limited area the size of a pin point and called it the "noeud vital" ("vital knot").

By applying the method of punctate stimulation and destruction of different portions of the medulla, Mislavsky established in 1885 that the respiratory centre is located in the reticular formation of the medulla on the floor of the fourth ventricle and that it is bilateral, each half being concerned with the innervation of respiratory muscles on its side of the body. Mislavsky also showed that the respiratory centre is a complex structure made up of *inspiratory* and *expiratory centres*. He concluded that a definite area of the medulla was the centre responsible for the control and co-ordination of respiratory movements; his conclusion has since been confirmed by numerous experiments, in particular by those more recently conducted using microelectrodes. Recordings of the electrical potentials of the separate neurones forming the respiratory centre revealed the presence of neurones that give rise to discharges at a much more rapid rate in the inspiratory phase, and others that produced discharges at a quicker rate in the expiratory phase.

Electrical stimulation at different points of the medulla with microelectrodes has also revealed neurones whose stimulation causes inspiration and others whose stimulation causes expiration.

Baumgarten demonstrated that the neurones of the respiratory centre are scattered in the reticular formation of the medulla close to the striae acusticae (Fig. 59). There is no distinct boundary between the inspiratory and expiratory neurones, but areas occur in which one or the other prevails (the inspiratory in the caudal portion of the tractus solitarius, and the expiratory in the nucleus ambiguus).

In experiments on warm-blooded animals Lumsden and others have found the respiratory centre to be more complex in structure than previously supposed. There is the so-called *pneumotaxic centre* in the upper part of the pons which controls the activity of the inspiratory and expiratory centres lying below, and maintains



**FIG. 59. Localization of the respiratory centres**

The drawing shows the lower portion of the brain stem (viewed from the back). PC — pneumotaxic centre; INSP — inspiratory centre; EXP — expiratory centre. The centres are bilateral, but to simplify the schematical representation only one is shown on each side. Section above line 1 does not interfere with respiration. Section along line 2 disconnects the pneumotaxic centre. Section below line 3 causes cessation of respiration

normal respiratory movements. The pneumotaxic centre stimulates the expiratory centre during inspiration and thus ensures rhythmical alternation of inspiration and expiration (p.205).

Integration of the activity of the neurones forming the respiratory centre is necessary to maintain normal respiration. Other parts of the central nervous system, located at a higher level, also take part in control by effecting fine adaptative changes to various forms of body activity. An important role in the control of respiration is played by the cerebral hemispheres and their cortex, which adapt the respiratory movements of man during talking, singing, physical exercise, and work.

**Automatism of the respiratory centre.** The neurones of the respiratory centre are characterized by automatism, which is evident from the fact that even after complete cessation of the flow of afferent impulses to the respiratory centre rhythmical oscillations of bio-electric potentials occur in its neurones, which can be recorded electrically. The phenomenon was first revealed by Sechenov in 1882. Much later Adrian and Buylendijk, employing an oscillograph with an amplifier, registered rhythmical oscillations of electrical potentials in the isolated brain stem of a goldfish. Kravchinsky encountered similar rhythmical oscillations of electrical potentials in an isolated frog's medulla with a frequency the same as that of respiration.

The automatic stimulation of the respiratory centre is attributed to the metabolic processes taking place within it, and to its high sensitivity to carbonic acid. The automatism of the centre is controlled by nerve impulses coming from the pulmonary receptors, vascular reflexogenic zones, and respiratory and skeletal muscles, by impulses arising in higher divisions of the central nervous system, and, finally, by humoral influences.

## CONTROL OF THE RESPIRATORY CENTRE

The respiratory centre is not only responsible for the rhythmical sequence of inspiration and expiration, but is capable of changing the depth and the rate of the respiratory movements, in this way adjusting pulmonary ventilation to the requirements of the organism at any moment. External environmental factors, like the composition and pressure of atmospheric air, the surrounding temperature, and changes in the state of the organism itself, e. g. with muscular work, emotions, etc., influence the intensity of metabolism and, consequently, the absorption of oxygen and the elimination of carbon dioxide, and in that way have an effect upon the functional condition of the respiratory centre. The volume of pulmonary ventilation alters as a result.

Like all other processes concerned with the control of physiological functions, the regulation of respiration occurs on the feedback principle. This means that the activity of the respiratory centre controlling the supply of oxygen to the body and the elimination of carbon dioxide produced in it is governed by the state of the process that is regulated. The accumulation of carbonic acid in the blood and oxygen deficiency are factors that stimulate it.

The importance of the blood gas composition in control of respiration was demonstrated by Frédéricq in experiments with cross-circulation. Two dogs were anaesthetized and their carotid and jugular veins were cut and joined (Fig. 60), and the other vessels of the neck clamped so that the head of each dog was supplied with blood not from its own trunk, but from that of the other.

Compression of the trachea in one of the dogs caused asphyxia, followed by arrest of respiration (*apnoea*) some time afterward, and was accompanied with severe *dyspnoea* in the other dog, which was explained by the fact that closure of the trachea in the first dog led to the accumulation of carbon dioxide in the blood flowing through the trunk (*hypercapnia*), and to a fall in its oxygen content (*hypoxaemia*). The blood passed to the head of the second dog and

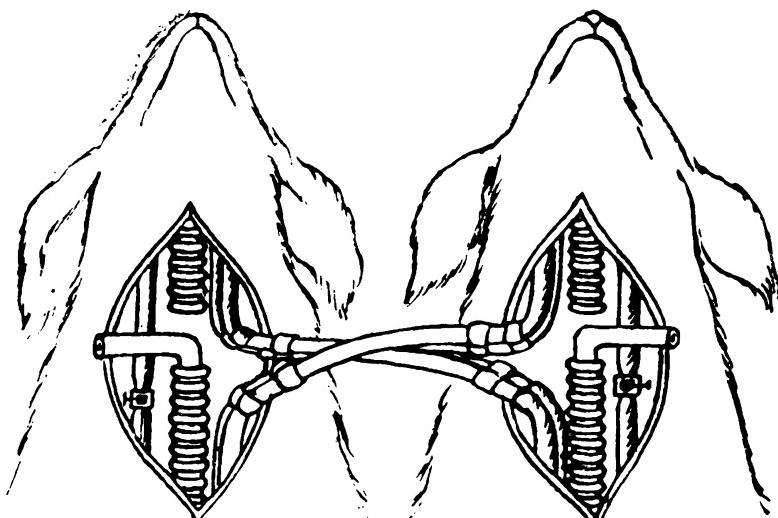


FIG. 60. Schematical representation of Frédéricq's experiment involving cross-circulation

stimulated its respiratory centre. As a result, augmentation of respiration, *hyperventilation*, occurred in the second dog, leading to a decrease in  $\text{CO}_2$  tension and an increase of  $\text{O}_2$  tension in the blood passing through its trunk. Blood rich in oxygen and poor in carbon dioxide flowed from the trunk of this dog into the head of the first dog, causing apnoea.

**Role of carbonic acid in control of respiration.** Frédéricq's experiment showed the activity of the respiratory centre to alter with changes in  $\text{CO}_2$  and  $\text{O}_2$  tensions in the blood. Changes in blood carbon dioxide tension were particularly important in that respect.

An increase in carbon dioxide tension stimulates the respiratory centre, leading to augmentation of pulmonary ventilation, while its reduction inhibits the activity of the respiratory centre resulting in a lowered ventilation. The role of carbonic acid was established by Haldane in an experiment in which a man was placed in a closed space of small volume. As the oxygen content of the inspired air fell and the carbon dioxide content rose, dyspnoea developed. If the carbon dioxide produced was absorbed by soda lime, the oxygen content of the inspired air could drop to 12 per cent with no noticeable increase in lung ventilation. Thus, the increase in the volume of ventilation in the experiment was caused by an excess of carbon dioxide in the inspired air.

In another series of experiments, Haldane determined the volume of pulmonary ventilation and the carbon dioxide content of alveolar air when a person was given a gas mixture with a varying carbon dioxide content to breathe. The results are reproduced in the table below. They show that a rise in the carbon dioxide content of the inspired air was attended with an increase in the amount of the gas in the alveolar air and, consequently, also in the arterial blood, so that pulmonary ventilation increased.

$\text{CO}_2$ content of inspired air, per cent	$\text{CO}_2$ content of expired air, per cent	Pulmonary ventilation, per cent
0.03	5.71	100
3.98	6.03	277
5.28	6.55	477

These experimental results have provided convincing evidence that the condition of the respiratory centre depends upon the carbon dioxide content of the alveolar air. It has been established that an increase by 0.2 per cent in this content leads to a 100 per cent increase of the pulmonary ventilation.

A fall in the carbon dioxide content of alveolar air (and, consequently, a decrease of gas tension in the blood) inhibits the activity of the respiratory centre, as occurs, for example, with artificial

hyperventilation, i. e. forced deep and frequent breathing that leads to a decrease in the partial pressure of carbon dioxide in the alveolar air and in the blood carbon dioxide tension. It results in cessation of respiration. The time that a person can voluntarily hold his breathing can be considerably prolonged in this way, i. e. by preliminary hyperventilation. Divers do so when they have to stay two or three minutes under water (respiration can usually be arrested voluntarily for 40 to 60 seconds).

Research into the way carbon dioxide affects the respiratory centre has shown that it stimulates respiration by excitation of the neurones of the respiratory centre both directly and reflexly, by causing excitation of chemoceptors lying in the vascular reflexogenic zones.

**Direct effect of carbon dioxide on the respiratory centre.** The direct stimulating effect of carbon dioxide on the respiratory centre has been established in various experiments. Injection of 0.01 millilitre of a solution of carbonic acid or of its carbonates into certain areas of the medulla causes an increase of respiratory movements. Euler exposed an isolated cat's medulla to the effect of carbon dioxide and found that it causes an increase in the rate of electrical discharges (action potentials), which pointed to excitation of the respiratory centre.

The appearance of frequent discharges in the centre was preceded by a gradual change in the membrane potential, resembling that encountered in the receptors. That can be regarded as evidence of the inspiratory neurones of the expiratory centre being susceptible to the effect of carbon dioxide and of their response being similar to that of peripheral chemoreceptors to certain chemical agents.

**Influence of an increase in hydrogen ion concentration on the respiratory centre.** In Winterstein's opinion, stimulation of the respiratory centre is caused not by carbonic acid itself, but by a rise in the concentration of hydrogen ions resulting from an increase of its content in the cells of the respiratory centre. This opinion is based on the fact that respiratory movements are augmented not only when carbonic acid, but also when other acids, like lactic acid, are introduced into an artery supplying the brain. Hyperventilation occurring with an increase in the concentration of hydrogen ions in the blood and tissues facilitates elimination from the body of some of the carbon dioxide in the blood, thus causing a drop in the ion concentration. The experiments provided evidence that the respiratory centre maintained not only a constant partial pressure of carbon dioxide in the blood, but also a constant concentration of hydrogen ions.

The facts established by Winterstein were confirmed in a number of experimental studies; his denial of the specific role of carbonic acid in the stimulation of the respiratory centre, however, proved erroneous. It was shown that carbonic acid exerted a higher stimulat-

ing effect upon the respiratory centre than other acids of an identical hydrogen ion concentration, so that most investigators have acknowledged the specific effect of  $\text{H}_2\text{CO}_3$  on the respiratory centre.

**Specific role of carbonic acid.** The respiratory centre is extremely sensitive to the effect of carbonic acid and  $\text{HCO}_3^-$  ions. This can be seen from the fact that respiration increases following introduction into the blood of alkaline bicarbonate which dissociates into  $\text{Na}^+$  and  $\text{HCO}_3^-$  ions in the blood and tissues.

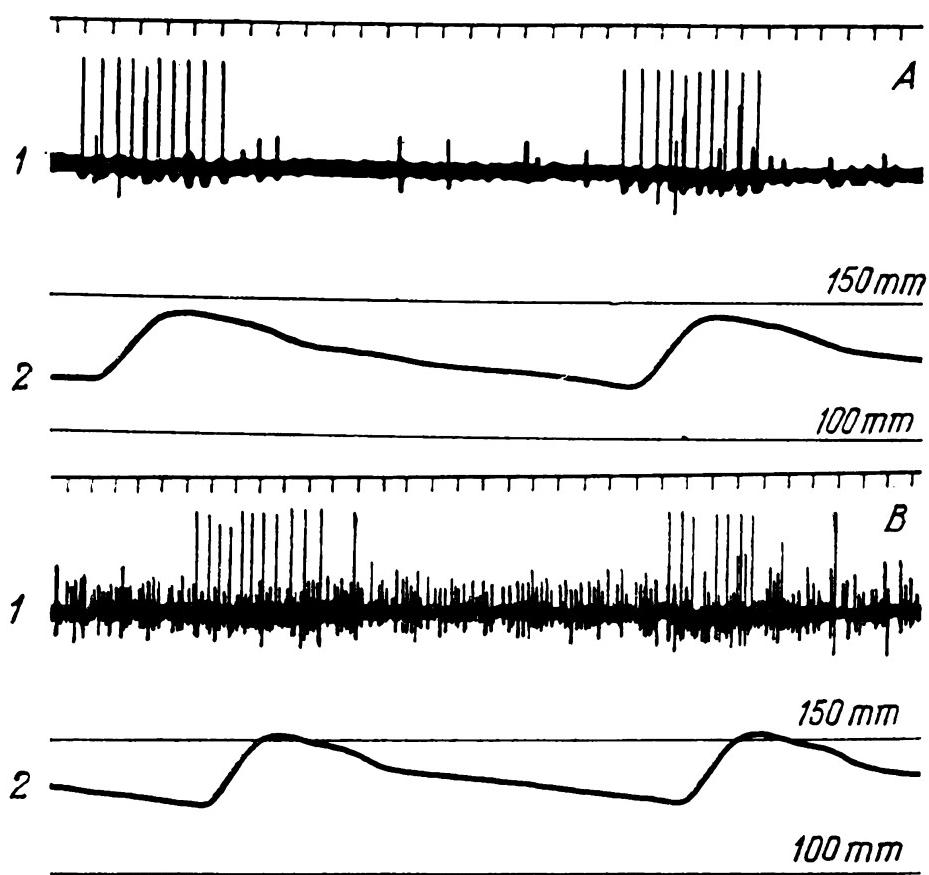
The specificity of carbonic acid as a stimulator of the respiratory centre was revealed experimentally by Jacobs who found that  $\text{H}^+$  and  $\text{HCO}_3^-$  ions pass through the cell membrane with difficulty, while undissociated carbonic acid penetrates it freely. His experiments gave grounds for supposing that the mechanism of the excitation of the centre by carbonic acid is as follows: undissociated  $\text{H}_2\text{CO}_3$  diffuses into the cells of the nerve centre where it undergoes dissociation, liberating the stimulating  $\text{H}^+$  ion. Its ability to diffuse into the cells more rapidly than other acids is the specific feature responsible for the more powerful stimulant effect of carbonic acid upon the respiratory centre.

The stimulating influence of carbonic acid upon the respiratory centre is utilized in clinical practice. With impairment of function of the centre and the associated oxygen deficiency the patient is given a mixture of oxygen with 6 per cent carbon dioxide (known as *carbogen*) to breathe through a mask.

**Reflex influence of carbonic acid on the respiratory centre.** As has been shown by Heymans, carbonic acid stimulates the respiratory centre both directly and reflexly through the chemoreceptors of the carotid reflexogenic zone. A rise in the carbon dioxide tension in the blood perfusing an isolated carotid sinus connected with the body only by nerve fibres leads to augmentation of respiratory movement; on the contrary, a decrease in carbon dioxide tension inhibits respiratory movement.

**Influence of oxygen deficiency on respiration.** Stimulation of the inspiratory neurones of the respiratory centre occurs not only with a rise in the tension of carbon dioxide in the blood but also with a fall in oxygen tension.

Oxygen deficiency causes a reflex activation of respiratory movement by affecting chemoreceptors of the vascular reflexogenic zones. Direct evidence of that stimulant effect of a decrease in the blood oxygen tension on the chemoreceptors of the carotid body was provided by Heymans, Neil, and other physiologists who recorded the bio-electrical potentials produced in Hering's nerve originating in the carotid sinus (p.149). Perfusion of the carotid sinus with blood poor in oxygen leads to an increase in the rate of action potentials in this nerve (Fig. 61). The respiratory changes caused by an excess of carbon dioxide in the blood differ in character from those encountered with a deficit of oxygen. A slight decrease in blood oxygen



**FIG. 61. Electrical activity in the sinus nerve (after Neil)**

**A** — when breathing atmospheric air; **B** — when breathing a gaseous mixture composed of 10 per cent oxygen and 90 per cent nitrogen; 1 — tracings of electrical activity of nerve; 2 — tracings of two pulse oscillations of arterial pressure. The calibration lines correspond to 100 and 150 millimetres mercury pressure levels. Tracing of action potentials shows a continuous flow of frequent impulses due to stimulation of chemoreceptors by oxygen lack. High-amplitude potentials occurring with a pulse rise in arterial pressure are caused by impulses arising in the pressoreceptors of the carotid sinus

tension is attended with a reflex increase in the rate of respiration, while a small increase in carbon dioxide tension is accompanied with a reflex augmentation of the depth of respiratory movement.

**The cause of the first inspiration in the newborn.** Exchange of gases in the foetus in the mother's womb occurs through the umbilical vessels, which are in close contact with the maternal blood in the placenta. The cessation of this communication with the mother at birth leads to an oxygen deficiency and excess of carbon dioxide in the blood of the child. According to Barcroft, that causes stimulation of the respiratory centre, resulting in inspiration.

For the first inspiration to occur, it is important that foetal respiration should cease suddenly; if the umbilical cord is compressed slowly, the respiratory centre will not be stimulated and the baby will die without taking a single breath.

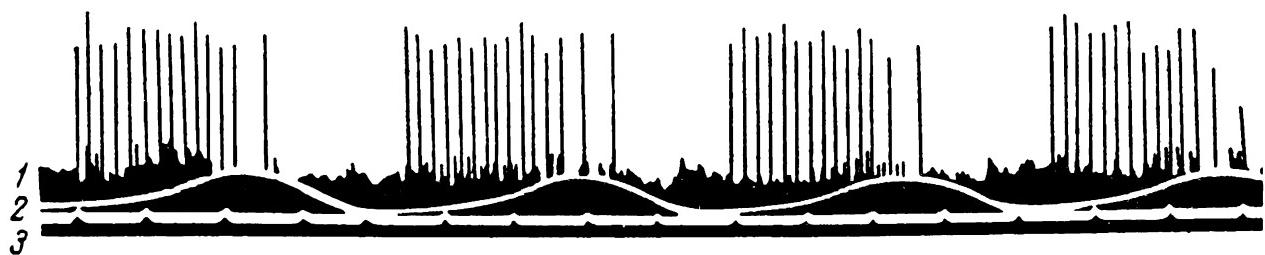
It should also be borne in mind that the change to the new conditions stimulates certain receptors in the newborn and a flow of impulses along the afferent nerves, which raises the excitability of the central nervous system, and of the respiratory centre (Arshavsky).

**Importance of mechanoreceptors in the control of respiration.** Afferent impulses reach the respiratory centre not only from chemo-receptors, but also from the pressoreceptors of the vascular reflexogenic zones, and from the mechanoreceptors located in the lungs, respiratory passages, and respiratory muscles. All these impulses evoke reflex changes in respiration. Those transmitted to the centre from the pulmonary receptors along the vagus nerves are particularly important as they greatly influence the depth of inspiration and expiration. The presence of reflex influences originating in the lungs was described in 1868 by Hering and Breuer and formed the basis for the concept of the *reflex self-regulation of respiration*, which is displayed as follows: with each inspiration impulses arise in the lungs, that reflexly inhibit inspiration and stimulate expiration, and with each expiration, impulses that reflexly stimulate inspiration. Several factors are evidence of the presence of such reflex control, viz. 1) there are interoceptors in the pulmonary tissue of the alveolar walls, i. e. in the most distensible part of the lung, that are endings of the afferent vagal fibres that perceive the stimulus; 2) cutting of the vagus nerves causes respiration to become much slower and deeper; 3) inflation of the lung with a neutral gas (e. g. nitrogen), providing the vagus nerves are intact, results in sudden cessation of contraction of the diaphragm and intercostal muscles, so that inspiration is arrested without having reached its usual depth; on the contrary, artificial aspiration of air from the lung causes the diaphragm to contract.

From those facts it was concluded that the distension of the pulmonary alveoli in inspiration stimulated the pulmonary receptors, which caused an increase in the rate of impulses conducted to the respiratory centre along the pulmonary branches of the vagus nerves, and that that in turn reflexly stimulated the expiratory neurones in the centre, and, consequently, resulted in an expiration.

By connecting the peripheral ends of cut vagus nerves with an oscillograph, electrical oscillations (action potentials) can be recorded both during inflation of the lungs and during artificial aspiration of the air from them. With natural respiration, however, frequent action potentials are registered in the vagus nerve only during inspiration and none during expiration (Fig. 62). Consequently, pulmonary collapse causes reflex stimulation of the respiratory centre only when the lungs are compressed to an extent not encountered in normal breathing as occurs with aspiration of air from them or with an acute bilateral pneumothorax to which the diaphragm responds by reflex contraction. During natural breathing the receptors of the vagus nerves are stimulated only on expansion of the lungs.

Mechanoreceptors lying in the intercostal muscles and diaphragm also take part in the control of respiration. Stimulation of the sensory nerves of the diaphragm or of the external intercostal muscles



**FIG. 62. Action potentials in the peripheral end of the vagus nerve arising on distention of pulmonary tissue in inspiration (after Adrian)**  
Top to bottom: 1 — impulses in vagus nerve; 2 — tracings of respiration (inspiration — upward deflation, expiration — downward deflation); 3 — time-interval marker

inhibits the activity of the inspiratory centre and excites the expiratory centre.

**Relations between inspiratory and expiratory neurones of the respiratory centre.** An intricate reciprocal relationship exists between the inspiratory and expiratory neurones, which means that stimulation of inspiratory neurons causes inhibition of the expiratory, while stimulation of the expiratory neurones inhibits the inspiratory. These phenomena are partly due to the existence of direct communications between the neurones of the respiratory centre, but are mainly caused by reflex influences and the activity of the pneumotaxic centre.

The view of the interaction occurring between the neurones currently held is as follows.

The direct or reflex (through the chemoreceptors) action of carbon dioxide upon the respiratory centre stimulates the inspiratory neurones, the impulses are conducted further to the motoneurones of the respiratory muscles, causing an inspiration.

At the same time, the impulse from the inspiratory neurones is conducted to the pneumotaxic centre lying in the pons, and passes from there along the processes of its neurones to the expiratory neurones of the respiratory centre in the medulla, causing excitation of those neurones, cessation of inspiration, and stimulation of expiration; excitation of the expiratory neurones in inspiration is effected reflexly as well by way of the Hering-Breuer reflex. If the vagus nerves are cut, impulses cease to flow from the pulmonary mechanoreceptors and the expiratory neurones may be excited only by impulses transmitted from the pneumotaxic centre. The flow of impulses that excite the expiratory centre diminishes markedly and its excitation is delayed somewhat, so that inspiration lasts much longer and expiration occurs later than before the vagotomy. The breathing will become slow and deep.

Similar respiratory changes are encountered when the vagus nerves are intact but the brain stem is cut at the pons, disconnecting the pneumotaxic centre from the medulla (Figs. 59 and 63). The flow of impulses acting on the expiratory centre also diminishes after

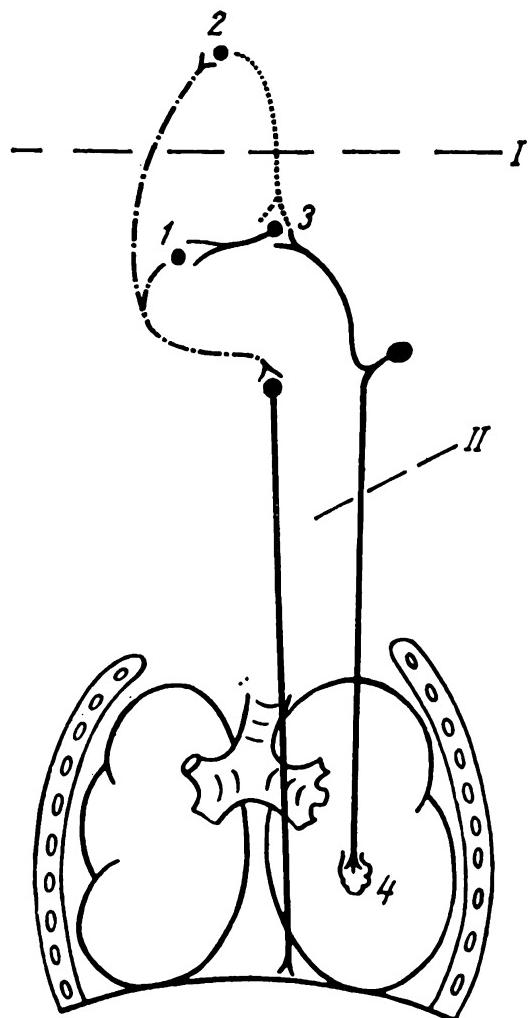


FIG. 63. Schematic representation of the respiratory centre nervous connections

I — inspiratory centre; 2 — pneumotaxic centre; 3 — expiratory centre; 4 — pulmonary mechanoreceptors. Sections made separately at levels I and II cause no changes in the rhythmical activity of the respiratory centre. Simultaneous section at both levels arrests breathing in the inspiratory phase

such a section, and respiration becomes slow and deep. The expiratory centre is then excited only by impulses from the vagus nerves. If, in addition, both vagus nerves are cut, or the flow of impulses along them is arrested by cooling them (Fig. 64), no excitation of the expiratory centre occurs and breathing ceases at the peak of inspiration. If the conductivity of the nerves is restored by warming, the expiratory centre will again be periodically excited and rhythmical breathing will resume (Fig. 64).

Thus, the vitally important function of respiration, which is possible only with a rhythmical succession of inspiration and expi-

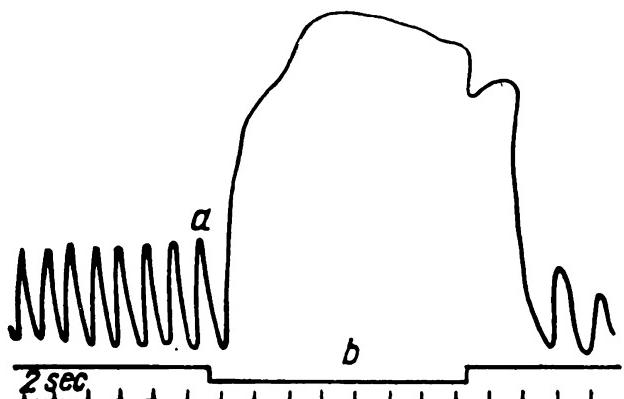


FIG. 64. Influence of vagi isolation on respiration following section of the brain between lines I and II (see Fig. 63) (after Stella)

a — tracings of respiration; b — marker showing cooling of nerves

ration, is controlled by an intricate nervous mechanism, studies of which have brought home that many factors are responsible for its action. The inspiratory centre, for example, is excited by both the direct and reflex effect of carbon dioxide, and through the influence of oxygen deficiency on the chemoreceptors. The expiratory centre is excited by reflex impulses reaching it along the afferent vagal fibres, and by the influence of the inspiratory centre effected through the pneumotaxic centre.

The excitability of the respiratory centre also alters under the influence of impulses arising in the pressor receptors of the vascular reflexogenic zones. A rise of pressure in an isolated carotid sinus connected with the body only by means of nerve fibres leads to suppression of respiratory movements. In the organism that is encountered with an increase in arterial pressure. Conversely, a decrease in arterial pressure is attended with an increase in the rate and depth of respiration.

Nerve impulses conducted by the cervical sympathetic nerve also alter the excitability of the respiratory centre; stimulation of that nerve increases it, so that respiration is augmented and its rate quickened.

#### DEFENCE RESPIRATORY REFLEXES

Irritation of the mucosa of the respiratory passages has a reflex influence on respiration. The reflexes produced are defensive in character, since they ensure the removal of the various irritating agents or prevent their entry into the lungs. Irritants, like ammonia vapour, for example, stimulate the sensory endings of the trigeminal nerve, arresting respiration in the expiratory phase. Simultaneously there is constriction of the bronchi innervated by the vagus nerve, which provides evidence that stimulation of the nucleus of the trigeminal nerve influences not only the respiratory centre, but also the vagal centre.

Dust and mucus accumulated in the respiratory passages, and foreign bodies, cause spasmodic expiratory movements by stimulating the endings of the laryngeal nerve. The glottis is closed at the beginning of each expiration, but as soon as a definite pressure is produced in the lungs and the respiratory passages, it opens suddenly and air is expelled with force from the respiratory passages. Thus a *cough* occurs, whose forcible thrust of air helps to clear the respiratory tract. If the receptors of the nasal mucosa are stimulated, reflex *sneezing* occurs; air is expired with force through the nose, clearing the nasal passages.

These defensive respiratory reflexes of sneezing and coughing are of essential importance as they contribute to the removal of foreign bodies from the respiratory passages and nose.

## ROLE OF THE CEREBRAL CORTEX IN THE CONTROL OF RESPIRATION

Apart from the medullary centres many other parts of the central nervous system, including the cerebral cortex, are concerned with the control of respiration. They differ essentially, however, in their role. The presence of the medullary respiratory centres is absolutely necessary for respiratory movements to occur and their destruction results in respiratory arrest. But respiration persists if a section is made at the higher parts of the central nervous system.

The particular role of the cerebral hemispheres is that they are responsible for the entire gamut of the finest adaptations of respiration to the requirements of the organism, associated with the continuously occurring changes in the conditions of its external environment and in its vital activity.

According to Sergievsky, the neurones of the cerebral cortex are more sensitive to an excess of carbon dioxide than those of the medulla oblongata and because of that the cortex may take part in the control of normal breathing by sending impulses to the respiratory centre.

The ability of the cerebral cortex to exert an influence on the processes of external respiration is well-known; both the rhythm and depth of the respiratory movements can be altered voluntarily, while breathing can be suspended for 30 to 60 seconds, or longer.

The influence of the cortex on the respiration was established in experiments involving the production of conditioned respiratory reflexes. Bekhterev and Protopopov were the first to observe the reflexes whose development caused changes in external respiration and gas exchange. Konradi produced conditioned respiratory reflexes by repeatedly giving air rich in carbon dioxide to a human subject, or an animal, to breathe. The act was preceded by a neutral signal, the ticking of a metronome. Repeated combination of the signal with the act gave rise to a conditioned reflex; pulmonary ventilation increased in response to the signal alone, as it had when air containing an excess of carbon dioxide was inhaled.

That the cerebral cortex influences respiration is also demonstrated by the fact that if an individual in a hypnotic state is persuaded that he is performing strenuous physical work, his respiration and gas exchange increase although he is still in a state of complete rest.

The possibility of respiration being altered due to conditioned reflexes explains why the breathing of athletes changes before the start of an event, becoming much deeper and more frequent. The importance of these changes lies in their adaptive character, since they help to prepare the athlete's organism for exertions that require the expenditure of much energy and an intensification of oxidation. The increase in the depth and rate of respiratory movement due to conditioned reflexes increases the volume of pulmonary ventilation, and the acceleration and augmentation of cardiac

contraction, which cause an increase in the cardiac output ensure the additional supply of oxygen required by the working muscles and the removal of eliminated carbon dioxide before carbonic acid and other metabolites formed during strenuous muscular exercise (lactic acid, etc.) accumulate in the blood. The conditioned reflexes that regulate respiration develop while an individual is being trained for definite physical effort. In trained individuals the mechanism of the conditioned reflex responsible for the control of respiration is quite perfect.

The controlling influence exerted by the cerebral cortex on respiratory movements during speaking and singing is of very great importance.

### PECULIARITIES OF RESPIRATION AND OXYGEN SUPPLY UNDER VARIOUS CIRCUMSTANCES RESPIRATION DURING PHYSICAL EFFORT

Since both respiration and circulation are concerned in satisfying the organism's requirements of oxygen and in removing from it the carbon dioxide formed, it is obvious that the intensity of respiration is closely associated with the intensity of the oxidative processes; the depth and rate of respiratory movement diminish at rest and increase during work, and the more strenuous the work, the greater the increase. Thus, the volume of pulmonary ventilation rises to 50 litres per minute and even to 100 (in trained subjects), during strenuous physical exertion.

Apart from the intensification of respiration, cardiac performance increases during work, leading to a rise in the minute volume of the heart. Both pulmonary ventilation and the cardiac output increase according to the volume of the work performed and intensification of oxidative processes.

The oxygen uptake of a resting individual varies between 250 and 350 millilitres per minute, and may reach 4,500 to 5,000 millilitres during work. It is possible to transport such a large volume because systolic volume can increase by 200 per cent during muscular exercise (from 70 to 200 millilitres), while the rate of cardiac contractions may double or even treble (from 70 to 150, or even to 200 beats per minute).

It has been calculated that with a rise in oxygen expenditure of 100 millilitres per minute during muscular exercise the minute volume of blood increases by 800 to 1,000 millilitres. The liberation of erythrocytes from the blood reservoirs and a reduction of the blood water content through sweating, which result in a certain thickening of the blood and a rise in haemoglobin concentration and, consequently, in an increase in its oxygen-carrying capacity, all contribute to greater carriage of oxygen. The coefficient of oxygen utilization increases markedly with muscular exercise. The body

cells use up between 60 and 80 millilitres of oxygen from each litre of blood in the systemic circulation when the organism is at rest, and up to 120 millilitres during work (the oxygen-carrying capacity of one litre of blood is about 200 millilitres). The passage of oxygen into the tissues increases because the drop in its tension in the working muscles and rise in blood carbon dioxide tension and H<sup>+</sup> ion concentration facilitate the dissociation of oxyhaemoglobin. The rise in oxygen utilization is particularly marked in trained individuals, which Krogh attributes also to the fact that a greater number of capillaries open in a trained subject during work than in an untrained person.

Another factor causing an increase in pulmonary ventilation and in the minute volume of blood is the accumulation of lactic acid in the tissues during strenuous effort and its passage into the blood, where its content may become as high as 50 to 100, or even 200 milligrams per 100 millilitres, as against five to twenty-two per 100 millilitres at muscular rest. Lactic acid displaces the carbonic acid attached to sodium and potassium ions, which leads to a rise in the carbon dioxide tension and to direct and reflex stimulation of the respiratory centre.

Lactic acid accumulates during muscular work because the strenuously working cells suffer oxygen deficiency and some of the acid cannot be oxidized to its end products, carbon dioxide and water. This condition, called the *oxygen debt* by Hill, occurs during vigorous muscular work, for instance in athletes during very close competition.

The oxidation of the lactic acid formed during muscular exercise and the resynthesis of glucose from it, are completed after the work has ceased, i. e. in the period of recovery during which forced respiration, sufficient to remove the excess lactic acid accumulated in the body, is maintained. The accumulation of lactic acid, however, is not the only cause of intensified respiration and circulation during muscular work. Marshak has shown that physical exercise gives rise to increased respiration even if the limbs of a subject working on an ergometer bicycle are compressed with a tourniquet to prevent passage of lactic acid and other products into the blood from the working muscles. Respiration increases reflexly; signals increasing respiration and circulation come from proprioceptors in the working muscles. This reflex component is always present in any increase of respiration during muscular activity.

With any frequently repeated muscular exercise, there is, along with these unconditioned reflex changes of respiration stimulated by muscular proprioceptors, an increase and acceleration of respiration induced by conditioned reflexes. The adaptative changes are produced by signals preceding the customary work and cause shifts that facilitate the performance of that work, i. e. give rise to a com-

plex of reactions that increase oxygen supply to the tissues and prevent the accumulation of lactic acid.

Thus, the increase in ventilation during muscular exercise is caused by chemical changes occurring in the body (accumulation of carbonic acid and incompletely oxidized products of metabolism) on the one hand, and by reflex influences, on the other.

#### RESPIRATION AT REDUCED ATMOSPHERIC PRESSURE

The problem of respiration at reduced atmospheric pressure is of great practical importance in high-altitude flight and mountain climbing. At heights of 4,000 to 6,000 metres symptoms of the so-called *mountain* or *altitude sickness* may occur, with signs characteristic of severe hypoxia. If the individual breathes a gas mixture with a high oxygen content through a face mask connected to a special cylinder, altitude sickness does not develop even at heights of 11,000 to 12,000 metres at which he could not exist without the additional oxygen supply.

At high altitudes the body suffers not only from oxygen deficiency, but also from a deficiency of carbon dioxide in the blood and tissues, i. e. from *hypocapnia*. The condition arises because oxygen deficiency in the blood stimulates the chemoreceptors of the carotid sinus and causes an increase in the rate of respiration, which in turn leads to the elimination of carbon dioxide from the alveolar air and, consequently, also from the blood. The deficiency of carbon dioxide reduces the excitability of the respiratory centre so that respiration does not increase enough to meet the oxygen requirements of the organism. The addition of a certain amount of CO<sub>2</sub> (up to 3 per cent) to the air breathed causes a marked improvement in an organism suffering from altitude sickness.

The possibility of raising the resistance of an individual to reduced atmospheric pressure by training is of great practical interest in connection with high altitude expeditions and flights and parachute jumping, e. g. of raising the "individual ceiling" of a pilot. The acclimatization of pilots and parachutists to high altitudes is carried out in special hermetic pressure chambers in which pressures like those encountered at different altitudes can be produced by exhausting the air from them. Training raises resistance to reduced atmospheric pressure, and subjects can retain their capacity for work even at a pressure of 316 millimetres of mercury, which corresponds to a height of 7,000 metres. At the same time, an untrained person placed in a chamber at a pressure of 355 millimetres (that encountered at a height of 6,000 metres) displays rapid and superficial breathing and indisposition after a short period and sometimes loses consciousness.

Acclimatization to reduced partial pressure of oxygen is encountered in individuals who have stayed at high altitudes for long periods, e. g. in people living in high altitude regions. It is caused by several

factors: viz. 1) by an increase in the number of erythrocytes in the blood and, consequently, by an increase in its oxygen-carrying capacity; 2) by an increase of pulmonary ventilation; 3) by a decrease of the sensitivity of body tissues, and particularly of the central nervous system, to oxygen deficiency.

The number of erythrocytes in the blood rises owing to intensification of blood formation and to the release into the circulation of blood from the reservoirs.

The growth in the number of reticulocytes, young types of erythrocytes, in the blood and the increase in the red marrow are evidence of intensified blood formation.

At a height of 15,000 metres the air pressure is 80 millimetres mercury. Under these conditions, the partial pressure of oxygen in the alveolar air remains much below the normal level even if a person breathes pure oxygen from an oxygen apparatus, and does not provide an adequate supply of the gas to the blood. For that reason, flights in the stratosphere and in space the more so, require hermetic cabins or individual space suits in which the pressure is maintained at the required level.

#### HYPOXIA

Deficient oxygen supply to the tissues is known as *hypoxia*, four types of which are distinguished: hypoxaemic, anaemic, stagnant, and histotoxic.

*Hypoxaemic hypoxia* is due to a deficiency in the amount of oxygen passing from the alveolar air into the blood, which may occur: 1) with low partial pressure of oxygen in the inspired air (at high altitudes, or when breathing artificial gas mixtures, or when in an enclosed space); 2) with deficient pulmonary ventilation, e. g. owing to obstruction of the respiratory passages, weakness of the respiratory muscles, failure of the respiratory centre (in poisoning), pneumothorax, etc. (the CO<sub>2</sub> content of the arterial blood rises in this type of hypoxia); 3) with deficient oxygenation of the blood owing to impaired diffusion of gases through the alveolar membrane, spasm of the bronchioles, and filling of the alveoli with fluid in pulmonary oedema, pneumonia, or drowning (the content of CO<sub>2</sub> in the arterial blood also rises); 4) with certain types of heart disease and anomalies of the large vessels, with what is called arterio-venous shunt when some venous blood by-passes the lungs and enters the systemic arteries, so reducing arterialization of the blood.

*Anaemic hypoxia* results from lowering of the ability of the blood to combine with oxygen, i. e. from a reduction of its oxygen-carrying capacity of the blood. It arises as a result of a low haemoglobin content (in anaemia); of the fixation of haemoglobin by other substances (in carbon monoxide poisoning, for example), or of the

production of methaemoglobin (in poisoning with nitrites, ferrocyanides, acetanilide, etc.).

*Stagnant hypoxia* is due to deceleration of blood flow in the capillaries in systemic circulatory failure (in cardio-vascular diseases).

*Histotoxic hypoxia* arises because of an inadequate supply of oxygen to the tissues themselves (in cases of inactivation of tissue oxidizing enzymes, encountered in cyanide poisoning, for example).

Hypoxia due to one of the first two causes above is marked by a reduced oxygen content, i. e. by a deficient oxygen supply to the blood. This condition, known as *hypoxaemia*, is not, however, encountered in hypoxia resulting from any of the other causes; the blood may be adequately oxygenated but the tissues still suffer a lack of it.

Hypoxia is attended with certain respiratory and circulatory changes of an adaptive character. A fall in blood oxygen content stimulates the chemoreceptors of the vascular reflexogenic zones, and produces a reflex increase of pulmonary ventilation, accelerates and increases cardiac performance and, consequently, an increase in cardiac output, a rise in the amount of circulating blood through discharge from the spleen and other blood reservoirs, and opening of the capillaries. The accumulation in the tissues of incompletely oxidized metabolites, that stimulate the respiratory and circulatory nerve centres, also contributes to the development of these phenomena.

If the factor responsible for hypoxia persists for a long time (prolonged residence at high altitudes, for example, or with certain types of cardiac disturbance), an adaptive increase in haemoglobin content and in the number of erythrocytes occurs.

In that way oxygen supply to the tissues is improved and hypoxia prevented. If, however, the adaptive changes in respiration, circulation, and blood composition are inadequate, the hypoxia will not be relieved and severe manifestations will appear, primarily symptoms of functional disorder of the central nervous system, which is particularly vulnerable to oxygen deficiency. Severe hypoxia is marked first by a condition like that encountered in alcoholic intoxication, and by hallucinations, then by convulsions, dimness of vision, dulling of consciousness, and finally, by unconsciousness. Respiratory and circulatory disorders develop at the same time owing to impairment of the centres responsible for their control, e. g. shallow breathing, and congestive phenomena in the vascular system displayed by *cyanosis* of the limbs, a weak pulse, and a fall in blood pressure. The disorders in respiration and circulation in turn impair the condition of the nerve centres even more, causing death rapidly in severe forms.

Only the hypoxaemic hypoxia resulting from reduced atmospheric pressure, of all the types of hypoxia discussed here, is met in healthy people and belongs to the phenomena with which physio-

logy is concerned. The remaining types of hypoxia are pathological and are the concern of pathophysioologists and clinicians.

#### PERIODIC RESPIRATION

A deficient supply of oxygen to the respiratory centre sometimes results in what is called *periodic* or *Cheyne-Stokes* respiration, which is characterized by the recurrence of pauses between groups of respiratory movements. The pauses may last from five to ten or twenty seconds or even longer. Each pause is followed first by weak respiratory movements and then by rapidly strengthening ones which, having reached a maximum volume, gradually, but quite quickly, become weaker until they cease completely; a new pause occurs, after which the whole cycle is repeated (Fig. 65). A cycle lasts between 30 and 60 seconds.

Periodic respiration is associated with reduced excitability of the respiratory centre resulting from oxygen deficiency and circulatory disorders confirmation of which is the fact that normal rhythm can often be restored by breathing pure oxygen.

A greater than normal amount of carbon dioxide and other acids has to accumulate in the cells of the insensitive respiratory centre in order to stimulate it. The additional accumulation occurs during the periodic pauses, and causes the appearance of strengthening respiratory movements, which increase the elimination of carbon dioxide. Since the content of carbonic and other acids in the respiratory centre in this condition drops below the level required to stimulate the centre, breathing wanes and ceases until a large amount of carbonic acid is again accumulated (Fig. 65).

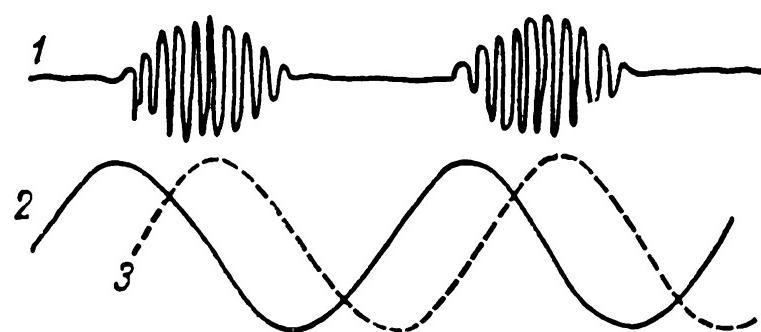
#### RESPIRATION AT INCREASED ATMOSPHERIC PRESSURE

Caisson miners and divers have to work at high atmospheric pressures. Gases dissolve in great amounts in their blood, tissue fluids, and tissues when they remain at depths at which the air pressure reaches ten atmospheres.

If they are *decompressed* gradually, as when a diver is brought to the surface slowly, gases escape from the body with expired air as the pressure decreases, and there is no danger. But if they are suddenly decompressed, i. e. if, for example, a diver is brought to the surface too quickly, the gases have no chance to escape and as their solubility in the blood decreases with the fall in pressure to normal, gas bubbles appear in the blood and can cause embolism of the vessels, i. e. they can block the vessels. As carbon dioxide and oxygen combine chemically with the blood, they are a lesser hazard than nitrogen which dissolves readily in fats and lipoids and accumulates in great amounts in the brain and nerves which are particularly rich in those substances. The condition caused by rapid decompress-

**FIG. 65. Periodic (Cheyne-Stokes) respiration**

1 — tracings of chest respiratory movements; 2 — blood carbon dioxide tension; 3 — carbon dioxide tension in cells of the respiratory centre



sion is called caisson or decompression sickness, and is characterized by pains in the joints and a number of cerebral symptoms: viz. dizziness, vomiting, dyspnoea, and unconsciousness. A sufferer should be treated by being exposed again quickly to the effect of high pressure so that the escaping gas bubbles dissolve again.

Divers working at great depths at present are given a gas mixture containing helium instead of nitrogen, as the former is almost completely insoluble in water and blood. Since oxygen is toxic at high pressures, it is added to the helium in concentrations such that its partial pressure at great depths, i. e. at increased pressure, will be that encountered under normal conditions. Besides, definite maximum rates have been laid down at which a diver, being brought to the surface or a worker leaving a caisson may be decompressed. In this way conditions have been provided for divers to work at depths of more than 100 metres, which was impossible with earlier techniques.

#### ARTIFICIAL RESPIRATION

*Artificial respiration* which ensures a certain degree of gas exchange is resorted to when lesions of the respiratory centre stop its functioning and arrest respiration.

There are three methods of artificial respiration: 1) rhythmic pumping of air into the lungs through the respiratory passages; 2) artificial rhythmic expansion and compression of the chest, imitating natural respiratory movements; 3) rhythmic electrical stimulation of the respiratory muscles.

The first method is that most widely used and consists in rhythmic supply of air to the lungs by means of a special bellows or pump operated manually or by a motor. Expiration is usually passive. Apparatus has also been proposed by which air can not only be introduced into the lungs but also aspirated from them. The simplest method, which can be applied in emergencies if no special apparatus is available, is mouth-to-mouth resuscitation, in which the person administering first aid periodically blows his expired breath into the patient's mouth, so inflating the latter's lungs. The oxygen content of the expired air (16 to 17 per cent) is sufficient to ensure normal gas exchange, while the high percentage of carbon dioxide

(3 to 4 per cent) facilitates stimulation of the patient's respiratory centre.

The second method of artificial respiration, that employing rhythmic compression or expansion of the chest, is used in various modifications. The simplest is the application of pressure to the chest with the hands at the rhythm of natural breathing. The chest expands passively each time the pressure ceases, and air enters the lungs. Prolonged artificial respiration is administered by means of the special apparatus known as the iron lung, which consists of a metal cylinder resembling a sarcophagus into which the patient is placed. The front end of the cylinder has an opening for the patient's neck and head, and is fitted with a special collar to seal it. As the patient's head protrudes from the cylinder atmospheric air has free access to the respiratory passages. A special compressor periodically raises and reduces pressure in the cylinder, rather in the way it is altered in Donders' experiment (p. 171). When pressure in the iron lung decreases, atmospheric air enters the lungs along the respiratory passages and causes the chest to expand. As pressure in the cylinder increases, the chest is compressed and air is expelled from the lungs. This method of artificial respiration can be employed for very long periods.

The third method is still in the experimental stage. It has been used successfully with animals but has not yet been widely introduced into clinical practice.

Apparatuses for applying artificial respiration are now connected to special devices that regulate their operation automatically according to the oxygen content of the blood. With a decline in the oxygenation of haemoglobin, the rhythm of artificial respiration rises and pulmonary ventilation is increased.

## Chapter 6

# DIGESTION

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### SIGNIFICANCE OF DIGESTION

Digestion is the complex physiological process by which food that has entered the alimentary tract undergoes physical and chemical changes and the nutrients in it are absorbed into the blood and lymph.

The *physical changes* in food consist in its mechanical processing by which it is ground, mixed, and dissolved. The *chemical changes* comprise a number of successive stages of protein, fat, and carbohydrate hydrolysis, occurring under the influence of *hydrolytic enzymes*. Three groups of these enzymes are distinguished: 1) those responsible for the breakdown of proteins, or *proteases*; 2) those responsible for the breakdown of fats, or *lipases*; and 3) those responsible for the breakdown of carbohydrates, or *carbohydrases*. The enzymes are produced in the secretory cells of the glands concerned with digestion and enter the alimentary canal as constituents of saliva and of the gastric, pancreatic, and intestinal juices. Any one nutrient is attacked by the various groups of enzymes, one acting after the other, and is gradually broken down into less complex chemical compounds.

Most of the substances contained in food—proteins, fats and carbohydrates—are high-molecular compounds that cannot be absorbed and utilized by the cells of the organism without being chemically treated in the alimentary tract. Only the simplest compounds, readily soluble in water and devoid of species specificity, which are

formed from them, can penetrate the wall of the alimentary tract into the blood. These include the breakdown products of proteins (amino acids and low-molecular polypeptides,), fats (di- and monoglycerides, glycerin, and salts of fatty acids), and carbohydrates (monosaccharides). Only water, mineral salts, and a small number of organic compounds present in food, enter the blood unaltered.

The main functions of the alimentary apparatus are secretion, movement, and absorption. The *secretory function* consists in the formation of digestive juices by gland cells: namely, saliva, gastric juices, pancreatic and intestinal juices, and bile. The *motor function* is effected by its muscles and is concerned with the mastication, deglutition, and movement of food along the alimentary tract, and the elimination of indigestible remains. *Absorption* is carried out by the mucous membranes of the stomach, and of the small and large intestines.

The organs of the alimentary tract perform not only a secretory function, but also an *excretory* one, expelling certain products of metabolism (e. g. bile pigments), and the salts of heavy metals, from the organism.

In Razenkov's view, the excretory function of the alimentary organs also consists in their eliminating a certain amount of protein which is then broken down to amino acids, absorbed into the blood, and used again by the cells to synthesize other proteins.

All the functions of the alimentary organs are regulated by complex nervous and humoral mechanisms.

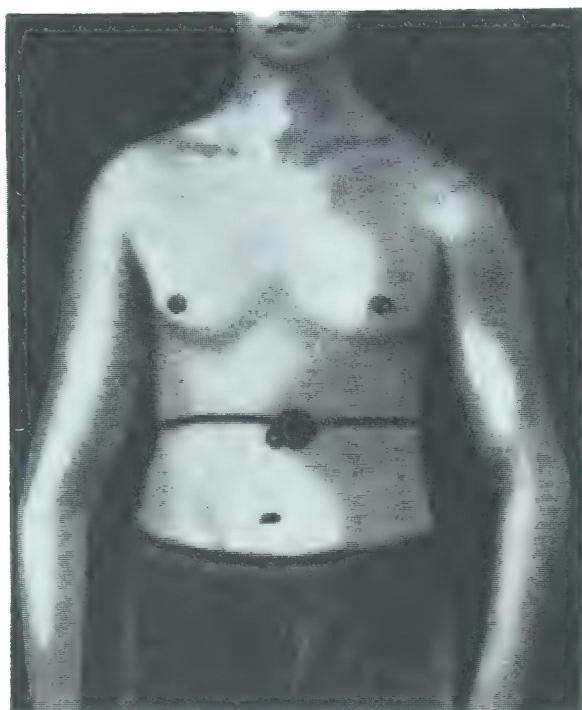
#### METHODS OF STUDYING THE FUNCTIONS OF THE ALIMENTARY TRACT

The principles of contemporary physiology of digestion were mainly elaborated by Pavlov and his pupils using an approach that was new in essence, and new techniques proposed by them.

Before Pavlov, the functions of the alimentary organs, that lay deep in the body and could not be observed directly, were mainly studied in acute experiments involving section of the living animal, in which the normal conditions of the organism were impaired by the trauma inflicted. After a Moscow surgeon, Basov, had proposed in 1842, studying the gastric secretion of a dog through a surgical fistula of its stomach, a number of researchers (Thiry, Vella, Klemensiewicz, Heidenhain) tried to investigate the functioning of separate organs in chronic experiments on animals previously operated on. (A *fistula* is a surgically created communication between a hollow organ — stomach, intestine, gall-bladder, or the duct of a digestive gland, and the external environment.)

Pavlov perfected the experimental surgical technique used to study these functions in chronic experiments. His approach consisted in an operation in a special operating theatre, observing all

FIG. 66. Gastric fistula in man



the rules and precautions required by surgery, to establish a fistula in some portion of the alimentary tract.

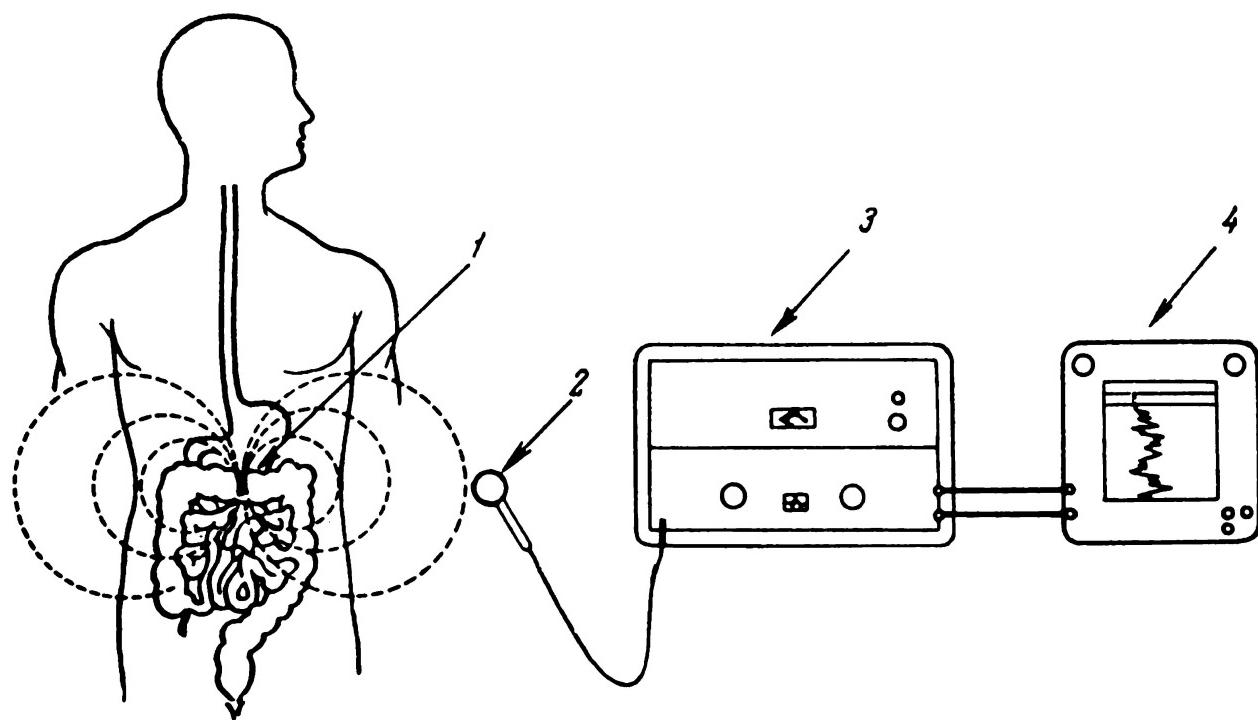
The fistula method enables the functioning of the organ operated on to be observed at any time; in addition normal circulation and innervation are retained.

Experimental studies on the animal are begun only after the surgical wound has healed and the animal's health and normal activity of the alimentary organs is restored. The fistula makes it possible to collect pure digestive juices containing no admixtures of food, to measure them accurately, and to determine their chemical composition at various moments of the digestive process, and thus follow the process of secretion. The fistula technique can also be employed to study the motor and absorption functions of the alimentary organs.

A great advantage of the method is the possibility it gives for stimulating the activity of the alimentary organs by natural stimulants and various nutrients.

The methods used to study the secretory and motor activity of the alimentary organs in man used to be extremely limited, and were confined to the introduction of a *tube* into the stomach and duodenum and X-raying of the contours of the stomach and intestine filled with some substance impermeable to X-rays. For obvious reasons, fistulas are not created in human subjects for research purposes, but they are sometimes encountered as the result of injury or of an operation performed for therapeutic reasons (Fig. 66).

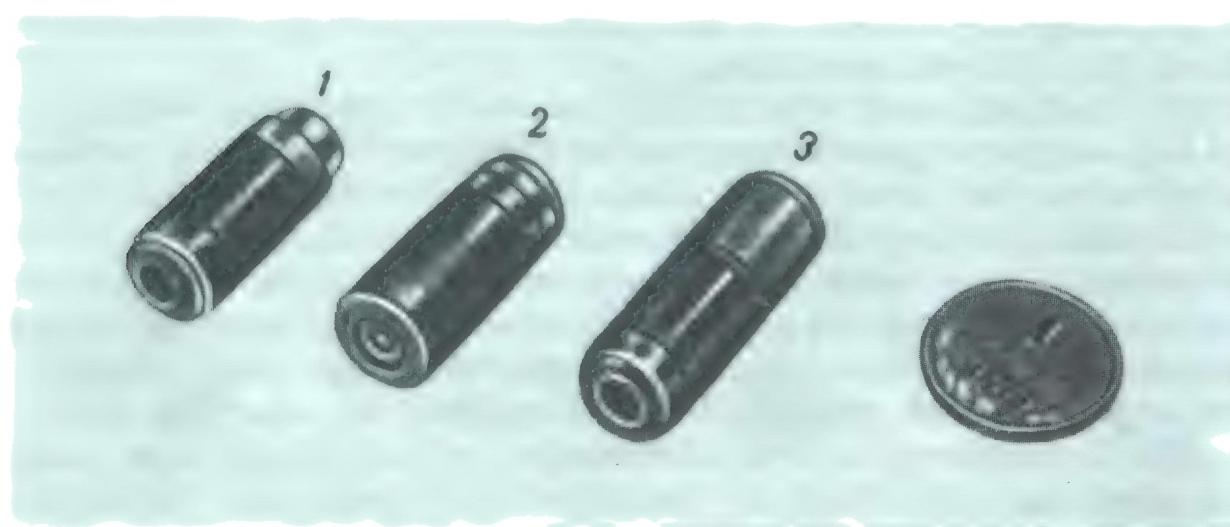
The development of radioelectronics has introduced new means for studying the activity of the digestive organs, like the method of *electrogastrography* (Sobakin) in which bioelectrical currents produced in the contracting smooth muscles of the stomach are record-



**FIG. 67. Schematic illustration of the operating principles of a radiotelemetric system used for studying the functions of the alimentary tract**  
**1 — radiopill emitting electromagnetic oscillations of a definite frequency; 2 — receiving antenna; 3 — receiver; 4 — recorder**

ed by electrodes on the skin of the abdomen connected to a constant-voltage or direct-current amplifier and an electrometer.

An effective research method is that employing *radiotelemetric techniques*. The subject is asked to swallow a miniature transmitter, or radiopill, about eight millimetres in diameter and from 15 to 20 millimetres long. The *radiopill* consists of a miniature radio-wave transmitter, a power supply, and a transducer that reacts to the H ion concentration in the contents of the stomach or intestines or to the pressure and temperature within those organs. Radiopills



**FIG. 68. Radiopills used for studying the temperature (1), pressure (2), and pH(3)**

are designed for studying one of those parameters through the changes it causes in the frequency of electro-magnetic waves emitted by the transmitter, which are picked up by an antenna and a radio receiver worn by the subject (Fig. 67). The radiopill moves freely along the alimentary tract and supplies continuous information on the degree of acidity or alkalinity, pressure, or temperature in the stomach and in all parts of the intestine (Fig. 68).

### DIGESTION IN THE MOUTH

The processing of food begins in the mouth where it is ground to small particles, moistened with saliva, and formed into a bolus. Food remains in the mouth of humans for about 15 or 18 seconds and is then swallowed, that is to say, is pushed into the pharynx and oesophagus by contractions of the muscles of the tongue.

While food is in the mouth, it acts as a stimulus on the taste, tactile, and temperature receptors. The taste receptors lie in the mucosa of the tongue, while the tactile, temperature, and pain receptors are distributed over the mucous membrane of the entire oral cavity. Impulses from these receptors are transmitted along the afferent fibres of the trigeminal, facial, and glossopharyngeal nerves, and reaching the nerve centres, reflexly stimulate secretion in the salivary, gastric, and pancreatic glands, and the motor acts of chewing and swallowing.

### MASTICATION

Mastication or chewing results from the contraction of the masticatory muscles that move the lower jaw against the upper. Being brought together by this movement, the upper and lower teeth tear, cut, and grind food.

Mastication is the mechanical processing of food, breaking it up into pieces and grinding it. At the same time it is mixed with saliva, softened and made fit to swallow.

### SALIVARY GLANDS

The ducts of three pairs of large salivary glands (the parotid, the submaxillary, and the sublingual), and of numerous small ones lying on the surface of the tongue and in the palatine and buccal mucosa, open into the oral cavity.

The salivary glands contain *mucous cells* that form a viscid secretion that draws out in threads, and *serous cells* whose secretion is fluid and watery and is called serous or protein saliva. The *parotid gland* and

the glands lying along the sides of the tongue, are formed of serous cells. Glands formed of mucous cells, the *mucous glands*, are situated at the root of the tongue and on the hard and soft palates. The submaxillary and sublingual salivary glands contain both the mucous and the serous cells and are therefore mixed. Mixed glands are also encountered in the buccal mucosa and in the mucous membranes of the lips and the tip of the tongue.

The salivary glands also have *myoepithelial cells* situated underneath the secreting cells; on their contraction saliva is squeezed out through the small gland ducts.

#### METHODS OF STUDYING SECRETION OF SALIVA

To study the activity of the salivary glands Pavlov suggested creating a *fistula of the excretory duct*. This was accomplished surgically as follows. The papilla of the duct of the parotid or submaxillary gland was separated from the surrounding tissues together with a portion of the mucosa, brought outside through a wound made in the cheek, and sutured to the skin. The secretion of saliva in an animal could thus be observed for many years (Fig. 69). A salivary duct fistula is occasionally encountered in man, following injury or certain diseases.

Saliva secreted by the submaxillary or parotid gland can be obtained in man through a small metal funnel, known as a *Lashley-Krasnogorsky capsule*, fastened to the mucous membrane at the opening of the excretory duct of the examined gland (Fig. 70).

#### COMPOSITION AND PROPERTIES OF SALIVA

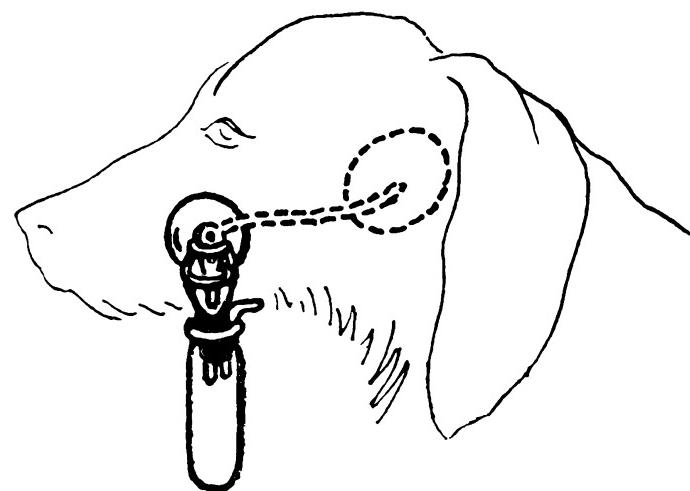
The consistency of saliva differs in various glands; the secretions of the submaxillary and sublingual glands are more viscid and thicker than those of the parotid. The difference in consistency depends upon the amount of *mucin*, a glycoprotein, present in the saliva. Mucin is responsible for the peculiar mucous appearance and lubricating property of saliva, which allows food saturated with it to be easily swallowed.

As well as mucin, saliva contains small amounts of globulin, albumin, amino acids, creatine, uric acid, and urea and inorganic salts. All these substances form a solid residue (0.5 to 1.5 per cent), about two-thirds of which is made up of organic substances and about one-third of mineral salts. Saliva has a weak alkaline reaction.

The amount and composition of saliva secreted by any one gland in a dog varies markedly according to the properties of the stimulus inducing secretion, i. e. depending upon the properties of the substances put into the mouth. Dry food, particularly if finely ground, is a powerful stimulus of the mouth receptors, and causes the secre-

**FIG. 69. Dog with a fistula of the parotid salivary gland**

A funnel and test tube for collecting the saliva are fixed to the cheek where the duct opening is brought to the outside

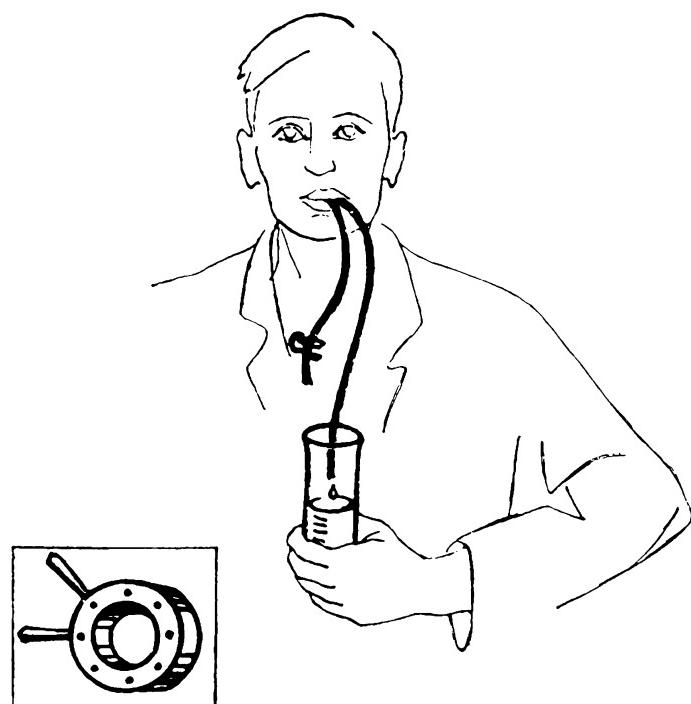


tion of greater amounts of saliva than does moist food. That is why rusks cause greater salivation than bread, and why more saliva is produced in response to powdered meat than to whole meat.

The content of organic substances, and of mucin in particular, excreted by the salivary glands of a dog eating any of the commonly given foods is four times that found in saliva produced when so-called rejected substances, e.g. river sand, hydrochloric acid, or bitters, are put into its mouth. The role played by saliva on introduction of rejected substances (i.e. those which the animal spits out) consists in diluting them, washing them off, and expelling them from the oral cavity. (According to Biryukov, the solid content of human saliva does not differ, as it does with dogs, with the different stimulants taken into the mouth.)

The daily amount of saliva secreted by man varies markedly according to the type of food, and averages between 1,000 and 1,200 millilitres.

**FIG. 70. Method for collecting human saliva by means of the Lashley-Krasnogorsky capsule. The capsule itself is shown at the bottom of the drawing**



**Salivary enzymes.** Human saliva contains enzymes that catalyse the hydrolysis of carbohydrates to dextrose. The enzyme called *ptyalin* (salivary amylase or diastase) converts starch into dextrins which are further broken down to form maltose, a disaccharide. Another salivary enzyme, *maltase*, breaks maltose down into two particles of dextrose.

Although the enzymes of saliva are highly active, they do not effect complete cleavage of starch because food stays in the mouth for a very short time. The optimum effect of ptyalin and maltase is exerted while a neutral reaction is maintained. A 0.01 per cent concentration of hydrochloric acid weakens their action, while higher concentrations delay it markedly and even destroy the enzymes, so that gastric juice suppresses their effect. Nevertheless, they may continue to affect the carbohydrates for some time even in the stomach because the bolus does not become impregnated with gastric juice at once.

#### CONTROL OF SALIVA SECRETION

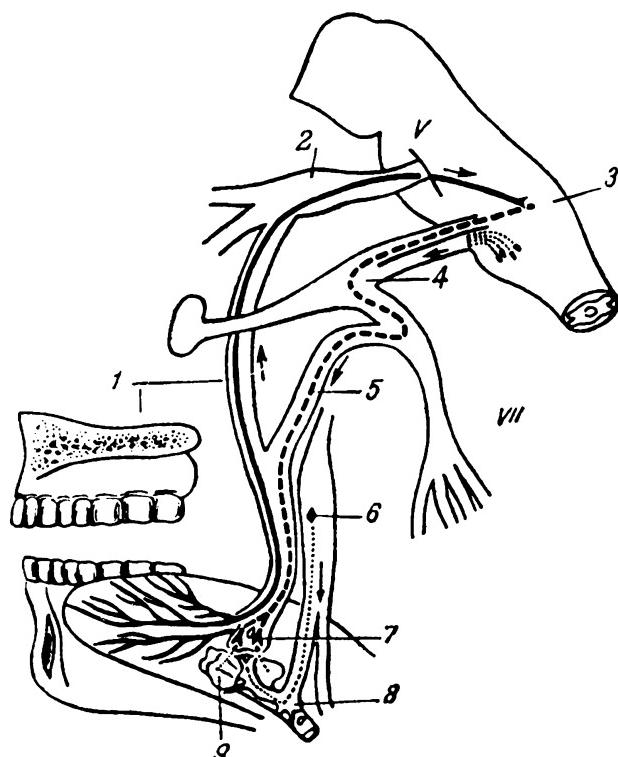
Secretion in the salivary glands occurs by reflex. The stimuli that give rise to unconditioned salivatory reflexes are foods or rejected substances which affect the receptors in the mouth.

With sufficiently strong stimulation, the secretion of saliva occurs within a few seconds. The interval between the introduction of the stimulant and the beginning of secretion is called the *latent period*; it may be as long as 20 to 30 seconds if the stimulation is weak. Saliva is secreted during the entire period that a stimulus is active, and stops soon after its cessation. The impulses that are produced by stimulation of the receptors in the oral mucosa are transmitted along the branches of the trigeminal and glossopharyngeal nerves to the medulla oblongata where the salivation centre lies in the region of the nuclei of the facial and glossopharyngeal nerves (Fig. 71). Electrical stimulation of this region causes a copious secretion of saliva. In Babkin's view, the medullary salivation centre consists of two parts, one sympathetic, the other parasympathetic, which innervate different cells of the salivary glands.

*Parasympathetic innervation* of the parotid gland is effected by secretory fibres in *n. glossopharyngeus*. The submaxillary and sublingual glands are supplied with parasympathetic secretory fibres by the chorda tympani, a branch of *n. facialis*.

Sympathetic innervation of the salivary glands is supplied by fibres arising from the superior cervical sympathetic ganglion, where there are postganglionic neurones that receive the impulses from the preganglionic neurones (see Vol. II, Chapter 16 on nerve regulation of vegetative functions) situated in the lateral horns of the spinal cord between the first and second thoracic segments.

**FIG. 71. Diagram showing the pathways of reflex stimulation of the submaxillary salivary gland**  
**1 — lingual nerve; 2 — gasserian ganglion which contains the sensory nerve cells; 3 — medullary salivation centre; 4 — fibres of facial nerve; 5 — chorda tympani; 6 — superior cervical sympathetic ganglion; 7 — submaxillary ganglion; 8 — artery and the accompanying sympathetic fibres supplying the salivary gland; 9 — submaxillary gland; V — trigeminal nerve; VII — facial nerve**



If the sensory nerves of the oral cavity or the secretory parasympathetic and sympathetic nerves of the salivary glands are cut, no saliva is secreted on ingestion of food or the introduction of rejected substances into the mouth. This furnishes evidence that the mechanism of salivary gland secretion is reflex in character. It has been established by histological studies that the parasympathetic nerve fibres in the chorda tympani innervate the mucous cells, and the sympathetic fibres the serous cells of the submaxillary glands (Fig. 72).

These special features of salivary gland innervation account for the differences in the composition of saliva secreted in response to various stimuli. The fact is that the stimulation of the two parts of the salivation centre, sympathetic and parasympathetic, produced by excitation of different receptors in the oral cavity is not the same. Efferent impulses arising in the salivation centre are transmitted to different cells of the salivary glands, so that the reflex saliva flow to various stimulants differs in character.

On excitation, the nerve endings of the secretory nerves of the salivary glands liberate mediators that stimulate secretion in the gland cells. Thus, excitation of the chorda tympani leads to the production of acetylcholine. Under normal physiological conditions this substance acts only at its site of liberation as it is quickly destroyed by cholinesterase, an enzyme present in the tissues and blood. Inhibition of cholinesterase activity by eserine prevents the destruction of acetylcholine, and it will then enter the blood and affect not only the organ in which it was liberated, but also other organs. Therefore in an animal given eserine, excitation of the chorda tympani supplying a certain salivary gland causes secretion in the other salivary glands also, and certain other physiological effects charac-

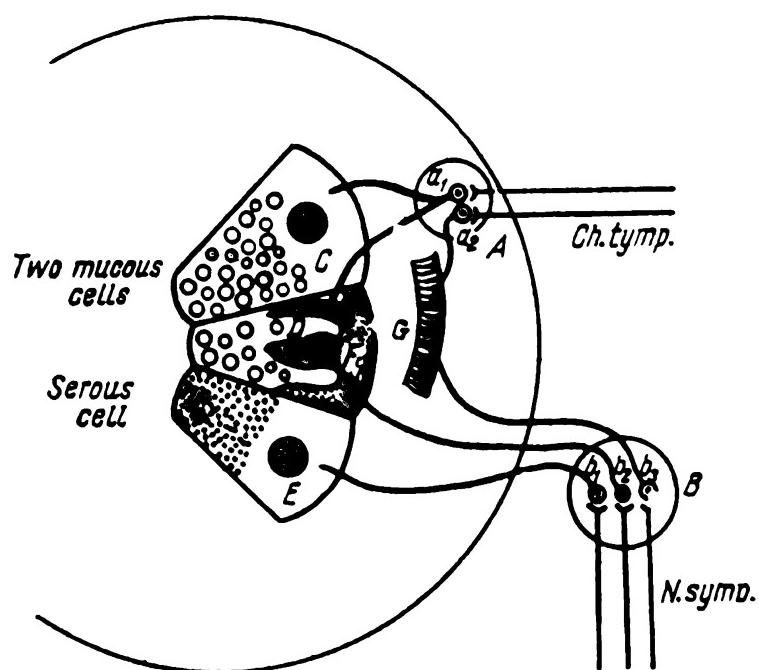


FIG. 72. Diagram showing the nerve supply to the cells of the submaxillary salivary gland (after B. Babkin)

A — sublingual ganglion;  $a_1$  — postganglionic parasympathetic neurone supplying the mucous cells (C and D);  $a_2$  — postganglionic vasodilator neurone supplying the blood vessel (G); B — superior cervical sympathetic ganglion;  $b_1$ ,  $b_2$ ,  $b_3$  — postganglionic sympathetic neurones supplying the serous cells (E), the myoepithelial cell (F), and the blood vessel (G)

teristic of acetylcholine (e. g. a fall in arterial pressure through decrease in the rate of cardiac activity and dilatation of the vessels).

Apart from acetylcholine, another vasodilator, *kallikrein*, is liberated in the tissues of the salivary glands following excitation of their parasympathetic nerves.

**Conditioned salivatory reflexes** produced in response to the action of visual, sound, smell, and other stimuli exist along with the unconditioned reflexes caused by excitation of the receptors in the oral cavity. Conditioned reflexes arise only if the action of the stimulus had previously coincided in time with feeding, which is why a conditioned reflex may cause secretion of saliva in an animal on the sight of food that it has eaten before, while the sight of new foods, edible but never tasted by it, will not produce a flow of saliva. When an acid solution has been introduced a number of times into the mouth of a human or of a dog, or after they have been given certain food several times, the procedures associated with these acts will by themselves evoke secretion of saliva. The secretion is then caused by stimuli, visual, sound, smell, etc., which have become conditioned stimuli of salivary secretion.

**Inhibition of salivary secretion.** Reflex influences can cause a decrease in secretion of saliva or even stop it. Reflex inhibition of secretion in the submaxillary gland has been encountered during excitation of the sciatic nerve, and when the intestinal loops are drawn out of the abdominal cavity through an incision. The delay in secretion of saliva in these experiments is attributed to the inhibiting effect of the pain stimulus on the salivary centre.

#### MECHANISM OF SALIVARY SECRETION

In a functioning salivary gland the blood vessels become dilated and blood flow increases. Thus, according to experimental data,

stimulation of the chorda tympani causes dilatation of the vessels in the submaxillary gland, and an increase of blood flow varying by 1.7 to 5.6 times the amount encountered during rest. Stimulation of the sympathetic nerve causes constriction of the gland vessels and blood flow is reduced to between 20 and 40 per cent of the normal amount; even total arrest of circulation in the gland is sometimes encountered.

The fact that copious secretion is usually attended by dilatation of the vessels of the glands does not give grounds to suppose that the secretion of saliva is due to filtration of fluid from the vessels into the gland ducts. It was long ago established in Ludwig's experiments that the secretion of saliva persists even when the pressure in the duct becomes higher than that in the artery feeding the gland. Thus, on stimulation of the chorda tympani, the pressure in the salivary duct may sometimes increase to double the blood pressure in the artery, which provides direct evidence that secretion of saliva cannot be attributed to filtration of fluid from the blood. If the production of saliva were due to filtration of substances in the blood, saliva and blood would have a similar content of salts and organic substances; in fact, however, they differ significantly.

The secretion of saliva results from the activity of the gland cells, for which the following facts are evidence. The uptake of oxygen in a gland during copious secretion is two to three times that in a resting gland. The temperature of a secreting gland rises, which points to an increase in energy expenditure in its cells.

Granules consisting of protein and enzymes (secretion granules) accumulate in large amounts in the cells of a resting salivary gland. They are produced by the cell organelles, in particular by the intracellular Golgi apparatus. Ribosomes consisting of ribonucleoproteins take part in the synthesis of the proteins produced by the cell. During secretion the granules collect within the cell at its apex, and are then discharged through the intracellular canaliculi into the gland ducts. Following copious secretion, the number of granules in the protoplasm of secreting cells falls sharply.

#### DEGLUTITION

Chewed food, moistened and lubricated by saliva, is formed into a bolus by movements of the cheeks and tongue and then placed on the upper surface of the tongue by the same movements. Contractions of the front part of the tongue press it against the hard palate, while a series of movements of the middle part push it to the back, forcing it past the anterior pillars of the faucet to the root of the tongue. Stimulation of the mucous membrane (root of the tongue) causes reflex contraction of the muscles that elevate the soft palate and of the tongue muscles. Raising of the soft palate prevents food from entering the nasal cavity. Tongue movements help to push the

bolus into the pharynx; simultaneous contraction of muscles that move the hyoid bone and raise the larynx causes the epiglottis to close the entrance to the larynx, so that food is prevented from entering the respiratory passages. The return of food from the pharynx to the oral cavity is obstructed by the elevated root of the tongue and the pillars, which are tightly pressed against it.

As soon as food enters the pharynx, muscles that cause constriction of its lumen above the bolus contract, and the bolus is passed into the oesophagus.

The act of swallowing (deglutition) involves a large number of muscles whose contraction is caused by sensory stimulation of the root of the tongue. It cannot occur unless food or saliva is present in the oral cavity, which can easily be demonstrated by swallowing a number of times in succession: the first time it is easy to swallow because there is always a certain amount of saliva in the mouth, but as it disappears swallowing movements become impossible.

Deglutition is a reflex act, effected by the following pathway: impulses from the endings of the sensory fibres in the trigeminal, glossopharyngeal, and superior laryngeal nerves are transmitted to the medulla; there, on the floor of the fourth ventricle, above the respiratory centre, lies a group of nerve cells that form the "deglutition centre". Impulses from the nerve cells of this centre spread along the motor fibres of the trigeminal, glossopharyngeal, hypoglossal, and vagus nerves, producing closely co-ordinated contractions of the muscles.

There is a complicated relationship between the deglutition centre and the other centres (respiration and cardiac activity) located in the medulla, which explains the occurrence of alterations in the activity of the heart and respiratory apparatus during swallowing: in man, for instance, each act of swallowing is attended with arrest of respiration and an increase in the rate of cardiac contraction.

Swallowing is an involuntary and automatic movement that occurs immediately a bolus reaches the entrance to the pharynx. Its reflex character has been established in experiments in which the sensitivity of the pharyngeal mucosa was suppressed by painting it with a cocaine solution — swallowing could not occur. Deglutition is also impossible after cutting the afferent pharyngeal nerves.

#### MOVEMENT OF FOOD IN THE OESOPHAGUS

As soon as a bolus enters the initial portion of the oesophagus, the oesophageal muscles begin to contract and the food is pushed towards the stomach. The movements are associated with those of the swallowing apparatus, which has been established by observations on humans. In a patient treated by section of the oesophagus,

the movement of food placed directly into it only starts after the patient has made swallowing movements.

Contractions of the oesophageal muscles are produced reflexly with each swallowing movement, and have the character of a wave that begins in the upper portion of the oesophagus and then spreads along its entire length. The wave is attended with successive contractions of the circular oesophageal muscles (striated in the upper third and smooth in the lower two-thirds of the oesophagus), which cause the bolus to descend.

The time needed for dry food to pass through the oesophagus averages between eight and nine seconds. Liquid food passes much more quickly, within one or two seconds, and there is then, as it were, a continuous column of fluid discharged with force from the oral cavity into the pharynx and oesophagus. Contraction of the latter apparently does not occur then.

The oesophagus is innervated by n. vagus, stimulation of which induces its movement. Cutting of both nn. vagi results in its partial paralysis. Experiments on cats have shown that movements in the middle and lower parts of the oesophagus, which have smooth muscular fibres, are restored within nine to 24 hours following bilateral vagotomy, while the upper part, formed of striated muscles, remains paralysed. Rehabilitation of movement in the lower part of the oesophagus is probably due to the presence of nerve cells in its smooth muscles. Sympathetic excitation also has a stimulating effect upon the oesophageal musculature.

The entrance to the stomach remains closed when swallowing movements are not made, but as soon as food moves along the oesophagus and distends it, reflex opening of the entrance occurs. Relaxation of the cardial muscles is also encountered during vomiting with forcible contraction of the stomach, abdominal muscles and diaphragm.

#### DIGESTION IN THE STOMACH

Having entered the stomach, food remains in it for several hours and only passes gradually into the intestine. The stomach plays the role of a "food reservoir" in which much of the food eaten is stored. Here also certain nutritive substances undergo chemical changes through the action of the juice secreted by the gastric glands.

The glands of the stomach lie in the mucous membrane of its fundus, corpus, and pylorus, with their ducts distributed over the mucosal folds in the form of tiny openings. The fundal glands are made up of chief, accessory, and parietal cells. The *accessory cells* produce a mucoid secretion; the *chief (adelomorphous, peptic, or principal) cells* produce the enzymes of the gastric juice (their rapid digestion after an animal's death is evidence of that); the *parietal (delomorphous, oxyntic, acid) cells* secrete hydrochloric acid. The

pyloric glands consist only of chief and accessory cells and contain no parietal ones (so that their juice contains no hydrochloric acid).

#### METHODS OF STUDYING GASTRIC SECRETION

Most of the information concerning the secretory function of the gastric glands was derived from experiments on dogs. Later observations on humans revealed that there is no significant difference between human secretion and that of dogs, so that the experiments on dogs acquired great significance for an understanding of human digestive processes.

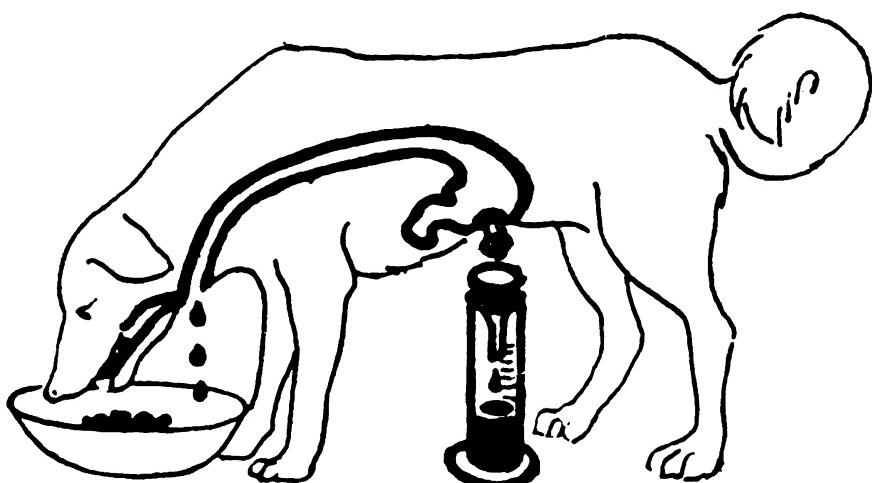
Experiments for research into gastric digestion involve the performance of various surgical operations on the animals. The simplest is the creation of a fistula. A *metal cannula* is inserted into the stomach through an incision in the abdominal and gastric walls, and fixed with sutures; its other end is brought to the outside and sutured to the skin. After the wound heals, stomach contents can be collected at any time through the cannula (between experiments the cannula is closed with a stopper). The cannula does not interfere with normal digestion and the animal may live for years.

It is not possible to collect pure gastric juice, and thus study the process of secretion, by means of this cannula because of the food and saliva that enter the stomach.

The disadvantages of the technique were overcome by supplementary operation made by Pavlov and Shumova-Simanovskaya in 1889; in addition to creating a gastric fistula, they also made a section of the oesophagus on the neck (Fig. 73). In this operation, known as *oesophagotomy*, the ends of the divided oesophagus were sutured to the skin wound.

After the oesophagotomy the animal could eat for hours without satisfying its appetite because the swallowed food did not reach the stomach but fell out through the neck opening. For that reason, feeding of this animal by the mouth was called *sham feeding*. The dog was fed either by introducing food directly into the stomach through the cannula, or by introducing liquid food by means of a tube into the peripheral end of the oesophagus.

The combined operation (fistulization of the stomach with section of the oesophagus) made it possible to study the reflexes induced in the gastric glands from the oral cavity and pharynx; but the technique did not permit investigation of the influence exerted on the gastric glands by food entering the stomach normally. That problem can be solved to some extent by experiments, involving the creation of an *isolated miniature stomach* or *pouch* as proposed by Klemensiewicz and Heidenhain. A small pouch is formed from a strip of gastric wall cut from the greater curvature, and its opening is sutured to the skin wound. The intactness of the stomach itself is restored by means of sutures. Two stomachs are thus formed: one large and



**FIG. 73. Oesophagotomized dog with gastric fistula**

normal, though made a little smaller by the operation, in which normal digestion occurs, and the other a small or isolated one into which food does not enter.

The pouch isolated by the Klemensiewicz-Heidenhain method is capable of secreting gastric juice some time after food enters the large stomach. The secretion, however, is not identical with the normal secretion of the gastric glands, as most of the nerve branches supplying the pouch are cut when it is created, and the first stage of juice secretion, that associated with nervous influence, does not take place.

Secretion of gastric juice from the thus isolated pouch begins 30 to 50 minutes after the ingestion of food, while in an oesophagotomized dog with a gastric fistula, in which the connections between the gastric nerves and the central nervous system remain intact, secretion begins five to ten minutes after sham feeding.

Pavlov suggested his own operative technique to form a pouch, that left the nerve supply intact and, consequently, enabled the secretion occurring in it to be observed under conditions closely resembling the physiological. A strip was made from the fundal portion of the stomach by an incision, as shown in Fig. 74, without interrupting the continuity of that part of the gastric wall, or, to be precise, of its serous and muscular coats, but completely dividing the mucous coat. Sutures were then applied to the mucosa on both sides, thus restoring the integrity of the large stomach and forming an isolated miniature stomach, the opening of which was sutured to the skin wound. The serous and muscular coats of the large and miniature stomach were sutured separately, and where they had been left intact they formed a bridge in the gastric wall between the two stomachs, along which the nerves supplying the isolated stomach passed (Fig. 75).

The secretion of juice in the Pavlov pouch was identical with that in the large stomach, and since food did not enter it, the gastric

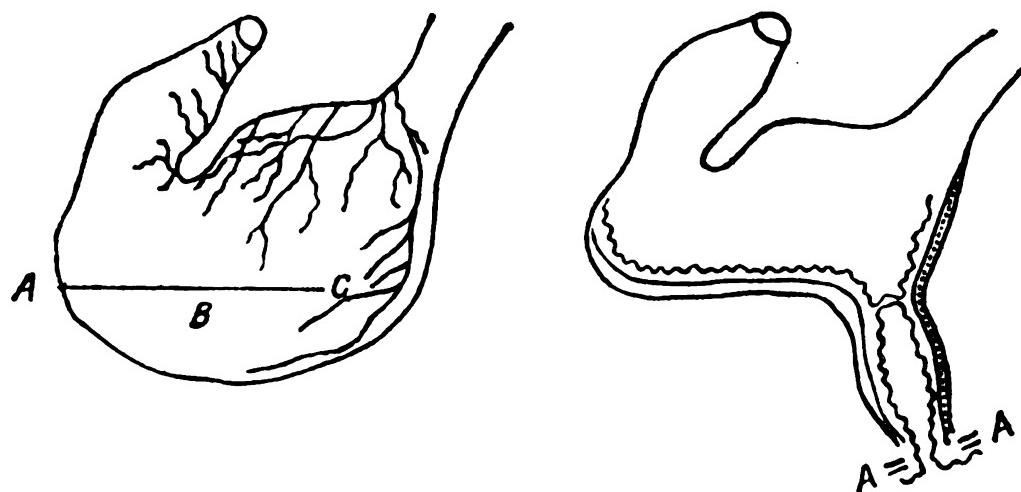


FIG. 74. Diagram showing incision for the creation of an isolated miniature stomach, or pouch, after I. Pavlov (left). Pouch formed as a result of the operation (right).

AC — line of incision; B — gastric wall from which the pouch is tailored; AA — abdominal wall. The branching lines indicate the passage of the vagi fibres

juice was free of foreign admixtures and its quantitative and qualitative composition could be studied.

A gastric fistula is sometimes also encountered in man as the result of an injury, or an operation for oesophageal obstruction (Fig. 66). Observations of the gastric secretion in a man who had a gastric fistula resulting from an accidental gunshot wound were described by Beaumont as early as 1834. Individual observations of gastric gland secretion were later conducted on individuals with a miniature isolated stomach formed as the result of a strangulated hernia.

The gastric secretion of human subjects is studied by introducing a rubber tube into the stomach. The examination is usually preceded by a test meal. The Boas-Ewald test meal is commonly given, consisting of 50 grammes of white bread and a glass of warm water.

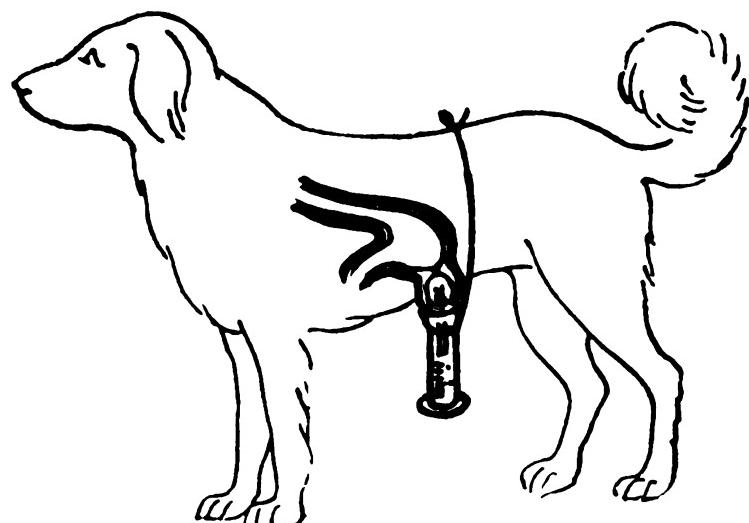


FIG. 75. Dog with an isolated pouch (after I. Pavlov)

Meat broth or cabbage juice, and solutions of alcohol or caffeine are also employed. A certain time after the meal has been eaten, the stomach contents are collected through the tube and chemically analyzed.

A new method is to use a tube with electrodes for electrometrical recording of hydrogen ions.

#### COMPOSITION OF GASTRIC JUICE AND THE BREAKDOWN OF FOOD IN THE STOMACH

Pure gastric juice is a clear colourless fluid with an acid reaction resulting from hydrochloric acid, which makes up 0.4 to 0.5 per cent of human gastric juice. The pH of pure juice is between 0.9 and 1.5; but with food in the stomach HCl concentration falls, and the pH varies between 1.5 and 2.5.

Gastric juice contains proteases which break down proteins to polypeptides of various complexity, and lipase which breaks down fats. The proteases include pepsins (one of which is formed in the chief cells of the fundus and the other in the cells of the pyloric glands), gelatinase, and chymosin (rennin). The *pepsins* only break down proteins in an acid medium (at a pH below 4; above 5.0 they become inactive). Maximum pepsin activity is exerted at two pH levels — 1.5 to 2.4 and 3.4 to 3.9. These enzymes have been isolated in a crystalline form.

Pepsins are secreted by the peptic cells in an inactive form, known as pepsinogens, which are converted into the active enzymes under the influence of the hydrochloric acid in the gastric juice. The *activation of pepsinogen* consists in the separation from it of a polypeptide containing arginine which suppresses the activity of pepsin.

*Gelatinase* breaks down gelatin, a protein contained in the connective tissue. *Rennin* and pepsin are responsible for the curdling of milk, i. e. for the conversion of the water-soluble protein caseinogen of milk into the protein casein which is insoluble in the presence of calcium ions.

The hydrochloric acid in gastric juice plays an important role in the digestive processes occurring in the stomach since it 1) provides the H ion concentration necessary for optimum pepsin activity; 2) converts pepsinogens into pepsins; 3) causes denaturation and swelling of proteins and in that way facilitates their breakdown by enzymes; and 4) contributes to the curdling of milk, i. e. to the conversion of caseinogen into casein by the pepsins and rennin.

*Lipase* causes the breakdown of fats to glycerol and fatty acids. In adults gastric lipase has no great importance since it acts only upon emulsified fats, but in infants it splits up as much as 25 per cent of milk fat.

The fats of human milk are broken down in the infant's stomach not only by gastric lipase, but also by the action of a fat-splitting

enzyme contained in the milk itself; the amount of lipase in cow's milk is insignificant.

Some researchers find that the lipase of human milk is activated by casein curdling, while others attribute it to a specific activator, *lipokinase*, present in the gastric juice of infants.

The splitting of polypeptides, begun in the mouth under the action of salivary enzymes, continues in the stomach. The duration and intensity of the enzyme action depends on how soon the food is mixed with gastric juice, whose hydrochloric acid inactivates the salivary ptyalin and maltase. Since the acid penetrates the inner layers of the ingested food slowly, and new portions of food occupy the middle of the stomach wedged, as it were, into the food ingested earlier, polypeptide splitting may go on for some time in the inner layers. A considerable part of the starch eaten by humans is broken down in the stomach by the salivary ptyalin.

Pavlov's observations showed that gastric juice had a constant concentration of hydrochloric acid, which was partly neutralized because the juice secreted by the fundal glands was mixed with food and the alkaline juice of the pyloric glands, which was why, the faster gastric juice was secreted, the less it was neutralized and the more hydrochloric acid it contained.

The juice secreted by different portions of the gastric mucosa varies in its digestive power and acidity; for instance, that secreted by the glands lying along the lesser curvature of the stomach has a high pepsin content and high acidity. The glands of this portion of the stomach are the first to begin and the first to stop secretion of juice.

#### JUICE FROM THE PYLORIC GLANDS

The juice produced by the glands of the pylorus is a thick, viscid alkaline fluid containing much mucus. In an empty stomach it is secreted at a rate of several millilitres per hour. Food entering the stomach causes mechanical stimulation of the pyloric mucosa and a significant increase in the flow of pyloric juice, and about 200 millilitres are apparently produced during the whole period of digestion.

#### ACTIVITY OF THE GASTRIC GLANDS IN A FASTING STOMACH AND AFTER EATING

Only alkaline mucus and pyloric juice are produced in the fasting stomach of a dog; but as soon as food is taken into the mouth, or visual, taste, smell, or other stimuli associated with receiving food act on the organism, the fundal glands begin to secrete acid gastric juice.

Examination of human subjects with a gastric fistula, and clinical observations, have provided evidence that scant, almost continuous



FIG. 76. Curves of gastric juice flow from a pouch after ingestion of meat, bread, and milk (after I. Pavlov)

secretion of acid gastric juice is maintained in the human stomach when no digestion is taking place. This feature of gastric secretion in man is accounted for by the fact that the intervals between taking food are usually short, as well as by the influence of psychic factors on the gastric glands. Secretion increases sharply after a meal.

Gastric juice varies in both amount and composition with the foods eaten. Experiments on dogs with a Pavlov pouch have shown that bread containing mostly carbohydrates, lean meat consisting mainly of proteins, and milk, in which proteins, fats, and carbohydrates are present together, evoke gastric secretions differing in quantity and in quality. Greater amounts of juice are produced in response to meat, and smaller amounts in response to bread and milk. Their ingestion is followed by a latent period after which gastric secretion begins; then the flow of juice increases rapidly and is maintained for several hours, falling off gradually. The characteristic curves of juice secretion in response to bread, meat, and milk are shown in Fig. 76.

Juice produced for meat contains more hydrochloric acid than that secreted for bread and milk. Enzyme content is highest after bread has been eaten.

Within certain limits, an approximately proportionate increase of secretion occurs with increase in the amount of food. The duration of secretion and the time during which food remains in the stomach also become longer as the quantity of food increases.

Fats inhibit the activity of the gastric glands for several hours following their ingestion; the digestive power and acidity of the juice fall, the latent period becomes longer, and the duration of secretion increases. After several hours inhibition is succeeded by excitation of secretory cells.

## PHASES OF GASTRIC SECRETION

It is customary to divide the period of gastric secretion into three phases. At the beginning of a meal secretion of juice is initiated by nerve impulses conducted to the stomach as a result of a reflex arising in response to the excitation of receptors in the mouth and pharynx (unconditioned reflex stimuli) and of receptors in the eyes, ears, and nose which are stimulated by the sight and smell of food and by sounds associated with its intake (conditioned reflex stimuli). The nerve impulses act as a trigger mechanism. The secretion of juice due to the act of eating proper constitutes the *first, cephalic, phase of gastric secretion*. We call it "complex-reflex" because it is induced by a complex of unconditioned and conditioned reflexes.

Under normal conditions of digestion, the reflex influences on the gastric glands of excitation of the receptors in the mouth and pharynx, and of those in the eyes, ears, and nose, are joined by the action of stimuli associated with the entry of food into the stomach. The food causes mechanical stimulation of the mucosa on the one hand, and the formation of substances in the stomach which, on being absorbed into the blood, excite gastric secretion through the humoral pathway, on the other hand.

The secretion of juice through these influences is referred to as the *second, gastric, or neuro-humoral, phase*.

Having been digested by the gastric juice, food gradually enters the intestine. Substances that stimulate the gastric glands are absorbed into the blood from the small intestine, and their humoral influence evokes the *third, intestinal, phase of gastric secretion*.

The **first or cephalic phase of gastric secretion** can be studied experimentally on an oesophagotomized dog with a gastric fistula in isolation from the other phases. The food fed to the dog falls out of its oesophagus and does not reach the stomach, but secretion of gastric juice begins five to ten minutes after this sham feeding.

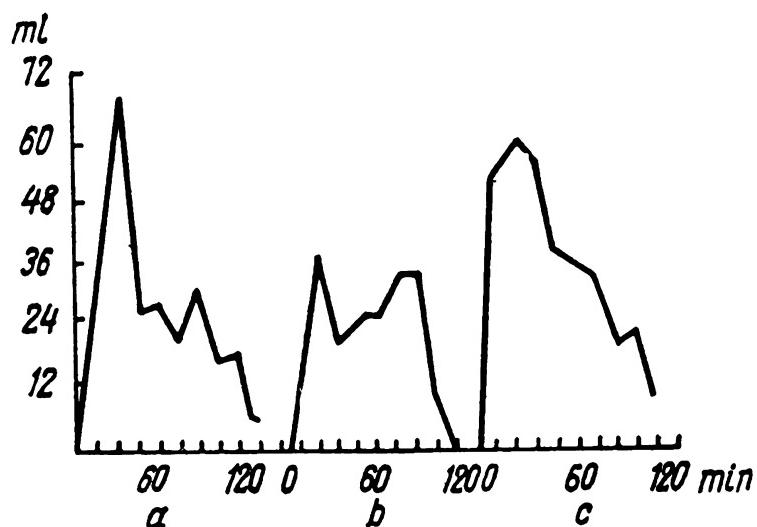
Similar data have been obtained from examination of human subjects who have had an oesophagotomy combined with creation of a gastric fistula for oesophageal constriction. Chewing and swallowing of food are attended by the secretion of gastric juice (Fig. 77).

Reflex gastric secretion occurs with sham feeding through stimulation of the receptors in the mouth and pharynx by the food. The reflex persisted in a dog whose cerebral cortex had been resected, which gave grounds for assuming that it was unconditioned in character.

Secretion may also be observed in a dog excited by the sight and smell of food (manifestations of a conditioned reflex are encountered here), but that does not occur in a dog whose cerebral cortex has been removed. While reflexes induced from the oral cavity and pharynx are inborn, those arising in response to visual and odour stimuli are acquired, as was demonstrated by Tsitovich who demonstrated in experiments that no gastric secretion occurred when

**FIG. 77. Gastric secretion in an individual following oesophagotomy and creation of gastric fistula (after I. Kurtsin)**

*a* — in sham feeding; *b* — on mechanical stimulation of gastric mucosa; *c* — on combination of sham feeding with mechanical stimulation of the stomach



meat was shown to a puppy several months old that had been raised on milk and bread, but that its gastric glands became active when meat juice was poured into its mouth or after it was fed with meat.

Gastric juice secreted during chewing or at the sight and smell of food was called appetite juice by Pavlov. Through it the stomach is prepared in advance for food.

Studies of human secretion have revealed patterns similar to those established experimentally. Observations of a twenty-year-old girl with an isolated stomach may be cited as an example. She had a gastric hernia (protrusion of the stomach under the skin through a defect in the abdominal muscles) which became incarcerated when she was one year old. A fistula was formed in a part of the stomach separated from the main stomach only by the mucous membrane in which the nerve and normal blood supply were retained. Acid gastric juice was discharged from the fistula, capable of protein digestion and milk curdling; secretion in the isolated stomach was stimulated by the very mention of tasty foods.

Similar phenomena have been encountered in individuals with a normal gastro-intestinal tract, from whom gastric juice was collected through a tube; conditioned reflex secretion of gastric juice occurred in these cases also at the sight of food or on hearing sounds associated with a meal (for example the sound of plates and forks being handled) (Fig. 78). The influence of the cerebral cortex on the gastric glands is well illustrated in experiments involving hypnosis: copious gastric secretion can be produced in a person who has been made to believe by suggestion that he has eaten an enjoyable meal (Fig. 79).

Reflex influences are conducted to the gastric glands by the vagus nerves. Neither sham feeding nor the sight and smell of food will start secretion in an oesophagotomized dog following bilateral vagotomy. The vagus nerve is the secretory nerve of the gastric glands. Strong electrical stimulation of the peripheral

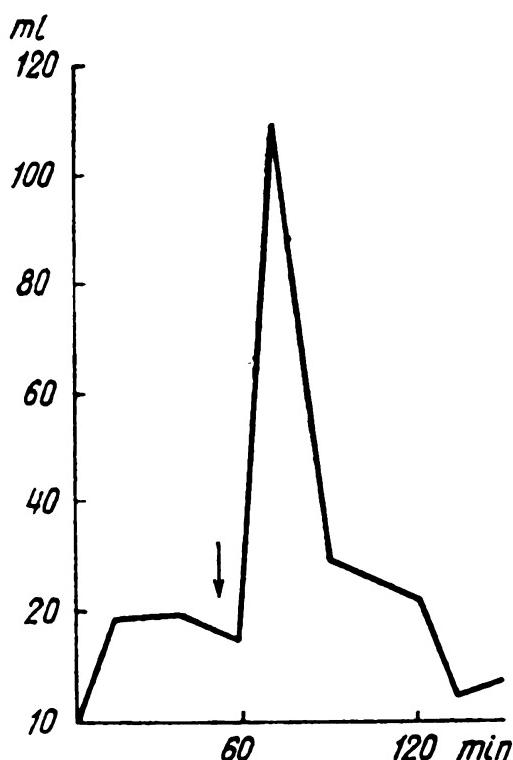


FIG. 78. Secretion of gastric juice in man, excited by a conditioned reflex (after I. Kurtsin). The arrow indicates the moment of conditioned stimulation

end of a previously cut (three or four days before the experiment) vagus nerve excites copious secretion of gastric juice with a high HCl content and high enzymic activity. On weak stimulation of the vagi nerves the gastric glands produce a small amount of mucus that gives a weak acid reaction.

Stimulation of the sympathetic splanchnic nerve inhibits the activity of the gastric glands.

Under particular experimental conditions, however, stimulation of the splanchnic nerve three or four days after it is cut or after

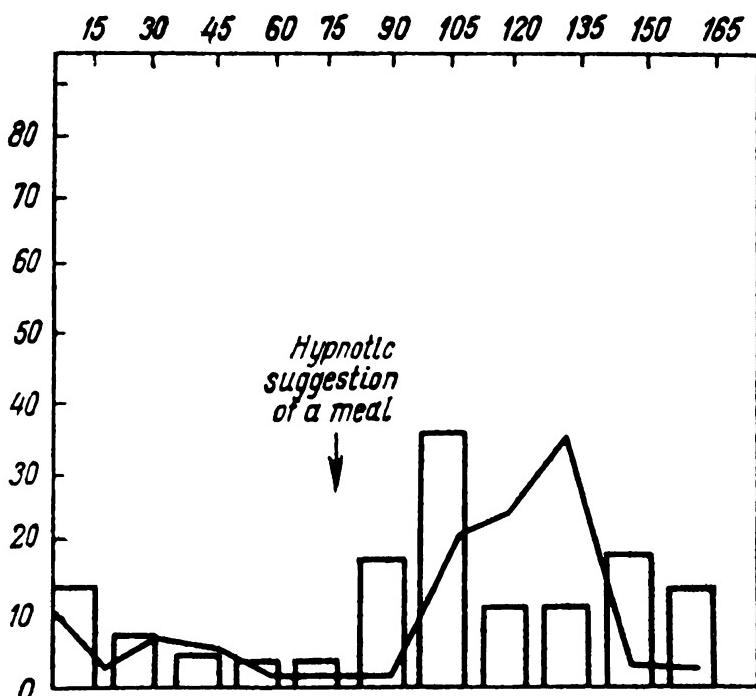


FIG. 79. Gastric secretion in an individual convinced by hypnosis that he had eaten a beefsteak (after I. Gordon).

Columns show the amount of gastric juice discharged from the gastric fistula; uninterrupted line shows the HCl content in the gastric juice. Figures in the upper part of the diagram mark off the time in minutes

painting the solar plexus from which it arises with nicotine, can demonstrate that this nerve evokes gastric secretion. In all probability the sympathetic splanchnic nerve also contains a small number of fibres that stimulate secretion, as well as inhibitory fibres.

**The gastric and intestinal phases of gastric secretion.** Sham feeding of short duration (eight to ten minutes) stimulates gastric gland activity for two to three hours, while the flow of gastric juice under normal conditions lasts for six to eight hours, or longer. Therefore, the whole period of gastric secretion cannot be attributed solely to reflex influences resulting from excitation of the receptors in the mouth and pharynx, and eyes, nose, and ears. The natural conclusion is that there is another mechanism concerned with their stimulation, which operates in the gastric phase under the influence of food entering the stomach, and in the intestinal phase of its passage into the intestine. Evidence of it is the fact that gastric secretion occurs without the excitation of the mouth receptors with food (for example if a piece of meat is put unnoticed into the stomach of a dog through a fistula). Then the latent period of secretion lasts 30 minutes and more, while the amount of juice secreted is one-half to one-third that produced in normal feeding. Certain foods, like meat broth, cabbage juice, and milk, initiate gastric secretion on being introduced into the intestine.

Excitation of gastric secretion on the entry of food into the stomach is effected by both mechanical and chemical stimuli, and on its entry into the intestine by chemical ones.

The effect of mechanical stimulation was demonstrated by Heidenhain and later by Ivy and Chechulin in experiments on dogs, and by Kurtsin through examination of human subjects. The insertion of a rubber bulb, strips of rubber, or glass beads into the stomach of a dog with a gastric fistula, which caused mechanical stimulation of the mucosa, excited a flow of acid gastric juice, with a latent period of secretion of 40 to 50 minutes. The latent period in man after mechanical stimulation is much shorter and lasts about five minutes. With continuous mechanical stimulation (by means of an inflated rubber bulb) up to 100 millilitres of gastric juice is secreted in an adult within one hour. In some experiments, with high excitability of the gastric glands, as much as a litre of juice has been collected over a period of three hours with this technique.

The composition and properties (acidity and digestive power) of gastric juice obtained by mechanical stimulation of the gastric mucosa in man are similar to those of the juice that flows in response to reflex excitation.

The secretion occurring on mechanical stimulation is started by a reflex arising from excitation of the receptors of nerve endings, mechanoreceptors, in the gastric wall. The reflex is suppressed by

cutting of the vagus nerves. Mechanical stimulation of the gastric wall also evokes humoral stimulation of secretion by causing the liberation of a chemical stimulator in the pylorus, which is absorbed into the blood and through it affects the gland cells.

The existence of humoral chemical stimulators affecting the secretory apparatus was established in experiments on dogs with an isolated Heidenhain stomach pouch. The reflex mechanism in the pouch was suppressed and only the humoral persisted as the vagus fibres to the part of the stomach from which it was formed were cut during the operation while circulation was left intact.

Secretion in the denervated pouch, which was cut off from communication with the central nervous system, began 30 to 50 minutes after the dog was fed. Secretion in the large stomach began earlier and the secreting activity of its cells was much higher than in those of the pouch. But in the following hours of digestion the intensity of the secretory process in the cells of both stomachs was the same.

Secretion in the pouch was caused by the liberation of chemical substances in the stomach during digestion, which entered the blood and stimulated activity of the gastric glands. Its low intensity in the first two hours was attributed to the fact that the reflex mechanism of secretion, which plays an important role in the period following feeding, could not affect the denervated pouch.

The presence of chemical stimulators in the blood was demonstrated experimentally by Razenkov. A dog was either fed with meat or milk, or a meat extract or cabbage juice was poured into its stomach. At the peak of gastric secretion 200 millilitres of blood were collected from the gastric artery and introduced intravenously into another dog whose gastric glands were at rest; the blood injection was followed by secretion of gastric juice. Thus, blood contains substances during digestion which provoke secretion in the gastric glands, while such stimulants are not present in the blood of a fasting animal.

According to Edkins' theory, a physiologically inactive substance, *progastrin*, is produced in the pyloric mucosa and converted into the physiologically active hormone *gastrin* by the hydrochloric acid in the gastric juice or by the products of digestion. Gastrin enters the blood flow and is carried to the cells of the gastric glands and stimulates their activity. An extract prepared from pyloric mucosa indeed initiates gastric secretion on being introduced into an animal's blood.

This theory is supported by observations that the removal of the pylorus results in a marked abatement or even disappearance of the second phase of secretion. Partial rehabilitation of the humoral mechanism occurs only long after pylorectomy, which indicates the specific role of the pylorus as the site of production of the humoral stimulus of gastric secretion.

The chemical nature of gastrin was established in 1964 by Gregory who succeeded in isolating from bovine pyloric mucosa two polypeptides that proved to be powerful stimulants of gastric secretion when injected subcutaneously into a dog. Their chemical structure has been determined. One, which stimulates gastric secretion in both man and dog, consists of 17 amino acids which are joined to one another in a definite sequence. Gregory and his co-workers synthesized an active preparation of gastrin. Copious secretion of acid gastric juice, and also of pancreatic secretion and stimulation of the motor apparatus of the stomach and intestine, are encountered after administration of this synthetic preparation. Gastrin was found to be five hundred times as active as the earlier known powerful stimulator of gastric secretion, histamine.

*Histamine* is a substance produced in the organism and contained in many foodstuffs. Very small quantities cause secretion in the gastric glands, fractions of a milligram being sufficient.

Histamine has been obtained from active extracts of gastric mucosa that stimulate gastric secretion, and also from meat and vegetable extracts. If the histamine in these extracts is previously broken down by exposure to enzymes, they then lose their ability to excite the activity of the gastric glands. *Histaminase*, the enzyme responsible for splitting histamine, is present in many organs of the body but is not contained in the stomach or the liver, so that histamine, being produced in the stomach in the course of digestion, is absorbed into the blood and exerts its secretory influence.

Histamine stimulates the parietal cells that secrete hydrochloric acid, but does not affect the chief cells concerned with the production of pepsin. Therefore, gastric juice obtained after the introduction of histamine into the blood is poor in enzymes but contains a high concentration of hydrochloric acid. There are data indicating that the acetylcholine produced in the endings of the vagus nerve liberates histamine which in turn excites secretion of hydrochloric acid by the parietal cells (Fig. 80).

In like manner the pyloric hormone gastrin may be liberated by the influence of impulses conducted along the vagus nerves (Bakuradze), which points to the existence of a close connection between the first, or reflex, and the second, or humoral, phases of gastric secretion.

Secretion can also be evoked by certain substances present in food, evidence of which is provided by the fact that the introduction into the blood stream of products of protein digestion, or extracts of meat or vegetables, i. e. substances that pass into the solution on boiling (for example, cabbage juice) initiates secretion in the gastric glands. These substances enter the blood from the intestine and cause secretion of gastric juice during the third, or *intestinal*, phase. In that phase secretion is also activated by *entero-*

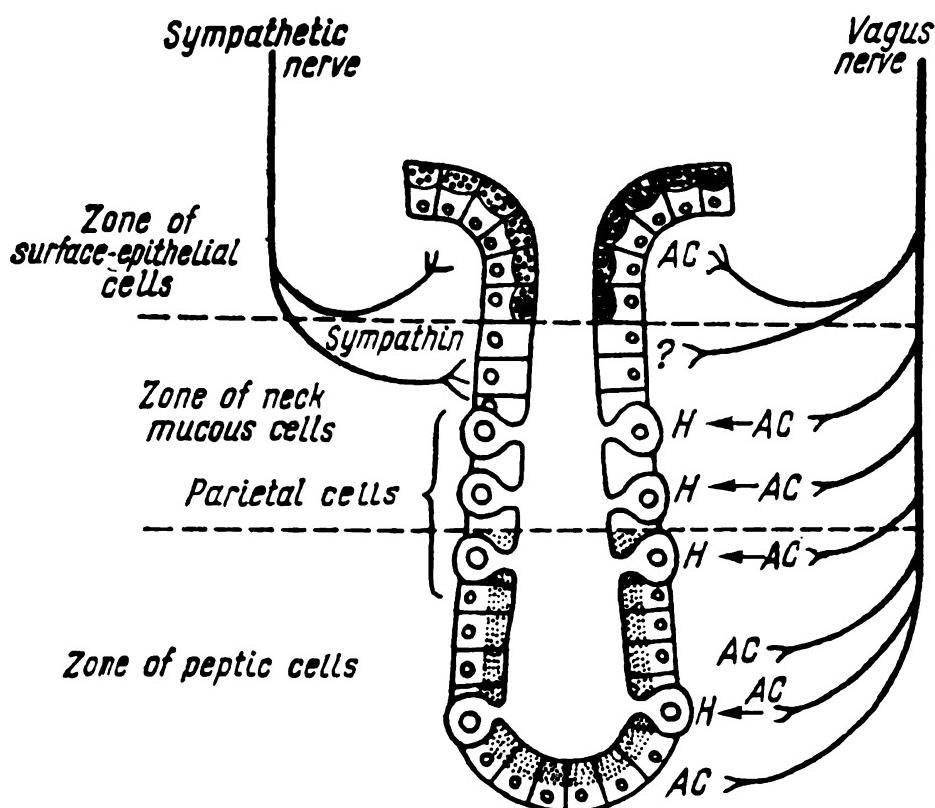


FIG. 80. Schematical representation of nerve supply to the cells of the gastric glands (after B. Babkin)

AC — acetylcholine formed in the vagal endings (it is assumed that it acts directly upon the pepsin and mucous cells);  $H \leftarrow AC$  — acetylcholine influencing the parietal cells through the mediation of histamine that is produced

*gastrine*, a substance produced in the mucous membrane of the duodenum. The existence of the intestinal phase accounts for the long duration of gastric secretion produced in response to humoral stimuli.

#### INHIBITION MECHANISM OF GASTRIC SECRETION

Gastric secretion is inhibited by a number of factors. Fatty food, for example, has an inhibitory effect on gastric secretion after entering the duodenum. The inhibitory effect of fat is attributed partly to its reflex influence, but mainly depends on the production of enterogastrone in the duodenum. The role of the nervous system in the inhibitory action of fats was demonstrated by Orbeli: in his experiments it becomes less marked in a dog following bilateral vagotomy.

Inhibition of gastric secretion is also encountered after large amounts of hydrochloric acid enter the duodenum, but only if the pH in the intestine is less than 2.5. Such a reduction of pH does not normally occur because the gastric contents pass into the duodenum in small portions and are rapidly neutralized by the alkaline intestinal juice. With excessive secretion (*hypersecretion*), however, the duodenal contents may become highly acid which

leads to inhibition of gastric secretion and, consequently, to a decrease in the amount of hydrochloric acid produced. The phenomenon can only be regarded as a compensatory adjustment of the organism, limiting excessive activity of the gastric glands.

An inhibitory influence of the nervous system on gastric secretion is encountered in emotional states, which is clearly demonstrated by the following experiment. If at the peak of gastric secretion produced by sham feeding a dog is infuriated by being shown a cat, the flow of juice is arrested for 15 to 20 minutes. Inhibition can also be caused by pain.

The inhibitory effect of emotions has also been observed in a human subject. A boy with a gastric fistula was teased for a long time with food; as a result of the negative emotions aroused (displeasure and anger) the next meal excited no gastric secretion.

The inhibitory effect of the nervous system in humans has been revealed as well in experiments on the effect of various odours and tests with hypnosis. The suggestion that food had an unpleasant taste caused a decrease in secretion. A similar result was observed when a subject smelt an extremely unpleasant odour during a meal. These data indicate that the state of the higher part of the central nervous system, the cerebral cortex, and the conditions in which a meal is eaten, are important to the activity of the gastric glands.

The mechanism of inhibition with certain emotions would seem to be stimulation of the sympathetic nervous system on the one hand, and a reflex increase in the secretion of adrenaline by the adrenals on the other (the sympathetic nerves and adrenaline have an inhibitory effect on gastric secretion).

Gastric secretion may also be inhibited by a substance produced by the intestinal mucosa, whose presence was established experimentally by Ivy, who found that an extract of the intestinal mucosa, freed of its many admixtures, reduced the flow of gastric juice on being introduced into the blood. It was supposed that this substance, *enterogastrone*, was absorbed in the intestine, and on being carried to the gastric glands by the blood inhibited their secretory activity. Enterogastrone is produced on the entry of fat and its breakdown products (fatty acids and their salts) into the intestine. It also has an inhibitory effect on the motor activity of the stomach.

Another inhibitor, *urogastrone*, has been found in urine. Whether it is identical with enterogastrone is not yet certain.

#### INFLUENCE OF DIET ON GASTRIC SECRETION

It was demonstrated, first in Pavlov's laboratory and later by Razenkov and his co-workers, that marked changes occur in secretion depending on the type of food given to an animal. Protracted

feeding (for 30 to 40 days) with food rich in carbohydrates (bread, potatoes, and vegetables) led to a decrease in secretion, and also to changes in the shape of its curve. But if the animal was given food with a high protein content, meat for example, for a sufficiently long period (30 to 60 days), then the amount of gastric juice increased, particularly during the second phase.

Not only the course of secretion but also the enzyme properties of the gastric juice are affected by different types of food. It has been established, for instance, that an increase in the amount of juice and higher acidity facilitate the digestion of animal protein, while a fall in its amount and acidity aid the hydrolysis of vegetable protein (Ugolev).

The influence of diet has also been confirmed by clinical studies. A fat-carbohydrate diet reduces gastric secretion in patients suffering from hypersecretion, which indicates the powerful influence of dietary measures on the functioning of the digestive glands.

#### MOTOR FUNCTION OF THE STOMACH

The *motor function* of the stomach is effected by contraction of the smooth muscle fibres forming its wall. Its purpose is to mix the stomach contents and to force food out of the stomach into the intestine. An important role in regulating that passage of food is played by the *pyloric sphincter* located at the end of the pylorus which closes the distal orifice of the stomach, and by the *prepyloric sphincter*, lying between the fundus and pylorus.

Various methods are employed to study gastric movements. One, the graphic method of recording, is as follows. A rubber balloon filled with water or inflated with air is introduced into the stomach and connected by a rubber tube to a Marey's capsule (Fig. 81). The gastric contractions exert a pressure on the balloon, which is passed to the capsule and raises its lever. The movements of the lever are recorded on a kymograph.

X-rays are the method widely used to study gastric movements in human subjects. For it the stomach has to be filled with a gruel-like mass of insoluble barium salt which is opaque to X-rays, as the gastric walls do not absorb the rays and for that reason cannot be seen on the screen of the X-ray apparatus. After a person has swallowed a barium meal a clear well-defined shadow is thrown onto the screen, whose shape changes with the contractions of the stomach.

Two types of relatively short and recurring contractions of the muscles are distinguished. The first is encountered after a meal, when acid gastric juice is secreted, with a rate of contraction of five to six per minute, and an amplitude between five and eight millimetres of mercury. It should be noted that contractions may not occur for the first hour and a half or two hours following a

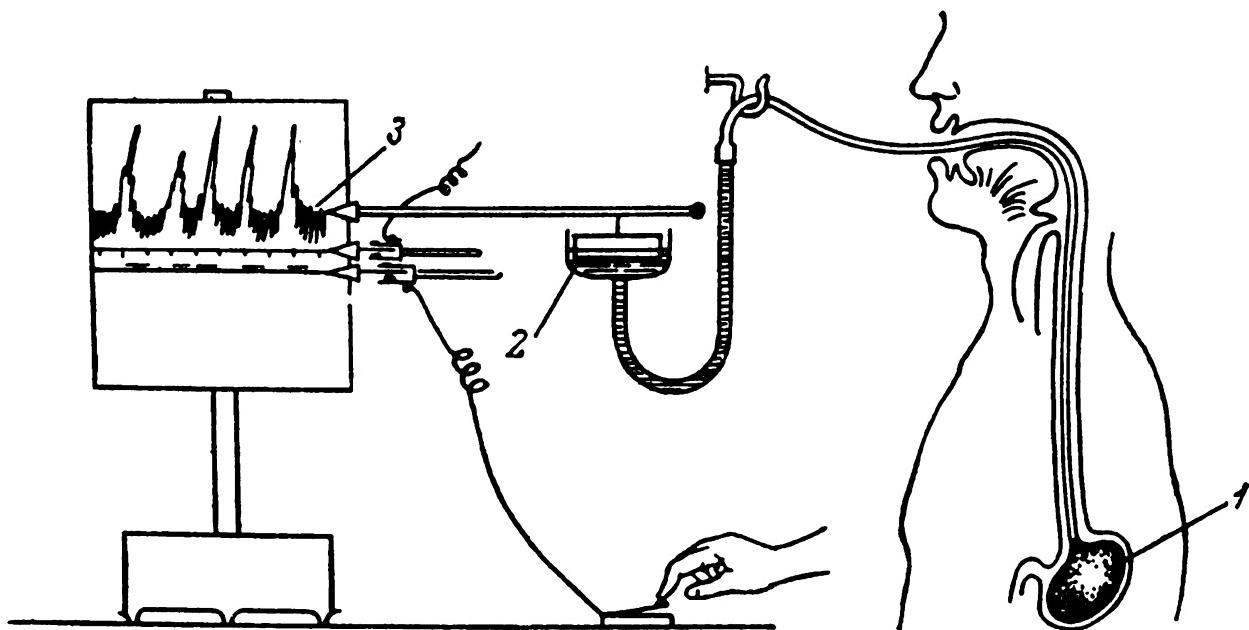


FIG. 81. Schematical representation of the device used for recording gastric movements in man (after Cannon)

1 — rubber balloon, inflated with air, introduced into the stomach and connected by a rubber tube to Marey's capsule (2); 3 — tracings of gastric movements on the kymograph

meal. The second type of contraction appears when food passes from the stomach into the intestine, i. e. during the so-called evacuation of the stomach, and also during the hunger contractions of an empty stomach (p. 275). It has slower pressure oscillations of wide amplitude. These contractions are weak in the fundus and two or three times stronger in the pylorus, where their pressure varies between 80 and 100 millimetres against 35 to 50 millimetres in the fundus. The contraction wave starts around the cardia, spreads to the pyloric sphincter, and lasts between ten and thirty seconds. In the limited area of gastric wall involved in the contraction wave, the circular fibres contract and the cavity of the stomach becomes smaller; the lower lying area, on the contrary, is distended. These contractions are always attended with pronounced bio-electrical potentials which can be recorded on an oscillograph from the abdominal surface.

In the ordinary normal conditions of digestion, the contractions result from the mechanical stimulation of the walls of the stomach by food.

Impulses via the vagus and sympathetic nerves are of the greatest importance to this motor activity. The vagus nerve mainly stimulates contraction (both force and rate), while the splanchnic nerve has an opposite effect, inhibiting gastric movement in most cases. The influence of these nerves is governed by the condition of the organ, in particular by the tone of its muscles. With a high tone, the vagus nerve may cause inhibition, while with a very low tone the sympathetic nerve is capable of stimulating movement. Bilateral vagotomy arrests gastric movements for several

hours and causes relaxation of the muscles, but contractility is restored later.

Humoral influences and chemical stimulation of the mucous membrane have a marked effect on gastric movement. The humoral agents that initiate contractions of the smooth muscles of the stomach are gastrin, histamine, choline, and  $K^+$  ions; entero-gastrone, adrenaline and noradrenaline, and  $Ca^{++}$  ions inhibit gastric movements.

The smooth muscles of the stomach possess automatism, i. e. their contraction can be excited in the absence of external stimuli. Evidence of that is the fact that a strip of the muscular coat put into a Ringer-Locke solution heated to  $37^\circ C$  continues to contract rhythmically for some time.

The muscular coat of the stomach contains many nerve cells forming Auerbach's plexus, which apparently participates in co-ordination of the contractions of the various groups of muscle fibres.

#### PASSAGE OF FOOD INTO THE INTESTINE AND THE PYLORIC OBTURATION REFLEX

The contractions of the gastric muscles force food from the stomach into the duodenum. The food that moves is the surface layer which passes along the lesser curvature until it reaches the pylorus, then leaves the stomach through the opening in the sphincter.

The rate at which food passes into the duodenum, i. e. the *gastric emptying time*, varies according to its amount, composition, and consistency and to the amount of gastric juice secreted. Food remains in the stomach for six hours, or even ten. Carbohydrates are evacuated more rapidly than food rich in proteins; fatty food is retained in the stomach for eight to ten hours. Fluids pass into the intestine almost immediately after entering the stomach.

The mechanism of gastric evacuation used to be attributed to the fact that the pyloric sphincter, open in an empty stomach, periodically closes and opens during digestion. Its opening is caused by stimulation of the mucous membrane at the exit from the stomach by the HCl of gastric juice. Some food then passes into the duodenum, and turns its contents from the normal alkaline state to acid. The acid acts upon the duodenal mucosa, causing a reflex contraction of the pyloric muscles, i. e. closure of the sphincter, so arresting the passage of food from the stomach. Once the acid is neutralized by excreted juices (pancreatic and intestinal secretions and bile) the intestinal contents again turn alkaline and the whole process is repeated. Since alkalinity persists over a considerable interval, a new portion of food leaves the stomach after the previous one has been adequately treated.

The closing of the pyloric exit through entry of hydrochloric acid into the duodenum is called the *pyloric obturation reflex*.

The reflex also occurs when fats are introduced into the duodenum, which explains why fatty food is retained in the stomach for a long time, since it causes the pyloric sphincter to close.

It has now been demonstrated, however, that the acidity of the gastric and duodenal contents is not the sole or determinant factor responsible for the passage of food into the intestine. Food leaves the stomach even when acidity is maintained for a long time in the duodenum (e. g. by introducing an acid through a fistula), while the introduction of an alkali causes no change in the rhythmic character of gastric evacuation. Similar observations have been made on human subjects. X-ray studies have shown that the duration of gastric evacuation is almost normal in individuals who have had a resection of the pyloric portion of the stomach.

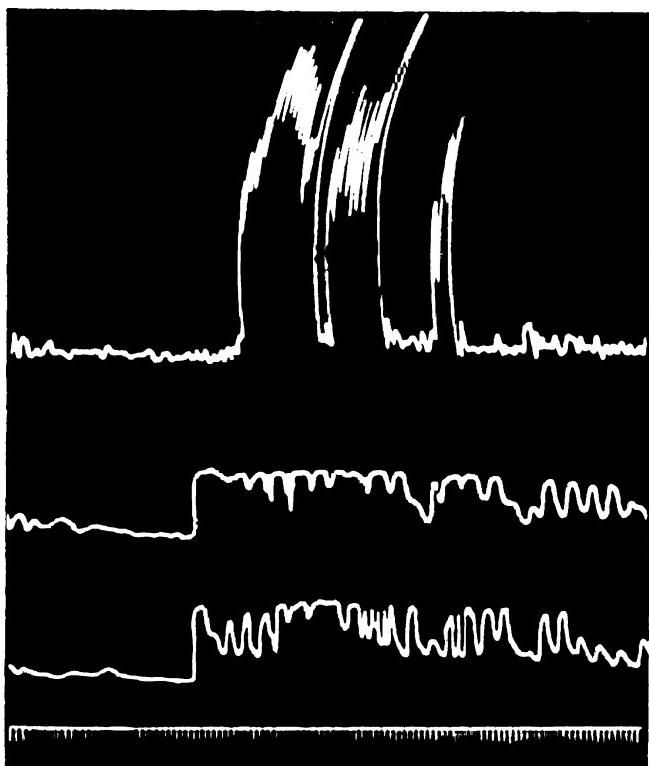
These facts all lead to the conclusion that it is not so much the rhythmical opening of the sphincter that mainly determines the evacuation of the stomach, as the contractions of the antrum pylori and of the whole gastric musculature.

The following factors are of importance to the passage of food into the intestine: 1) the consistency of the gastric contents; 2) their osmotic pressure; 3) how full the duodenum is. The gastric contents enter the intestine as soon as they acquire a fluid or semi-fluid consistency. The role of the osmotic pressure is clear from the fact that hypertonic solutions inhibit evacuation and leave the stomach only after they have been diluted by gastric juice to an isotonic concentration. Distention of the duodenum also delays evacuation and can even cause its temporary arrest. The evacuation is controlled by the nervous system and humoral factors. The existence of the latter is demonstrated by the fact that entero-gastrone, secreted by the intestinal mucosa under the influence of fats and fatty acids, inhibits gastric movement and evacuation.

#### VOMITING

Vomiting is a motor act involving the gastrointestinal tract, that occurs reflexly on stimulation of sensory nerve endings or due to substances (for example, apomorphine) that directly affect the nerve centre when carried in the blood. Vomiting can be induced by stimulating various organs, for example, the root of the tongue, the pharynx, the mucous membrane of the stomach, the intestine, the abdominal cavity, and the uterus; it can be stimulated as well by smells or tastes that give rise to revulsion (conditioned reflex vomiting).

Vomiting is a complicated, co-ordinated series of movements that begin by a contraction of the muscles of the small intestine (Fig. 82), leading to regurgitation of part of the intestinal contents into the stomach. Ten to twenty seconds after the intestinal phase,



**FIG. 82.** Tracings of vomiting movements (after E. Babsky)  
The upper tracings record gastric movements, the second tracings from the top, duodenal movements, the third tracings, the movements of the small intestine; the bottom line is the time-interval marker

the gastric muscles contract, the entrance into the stomach opens, and violent contraction of the muscles of the abdomen and diaphragm occurs, by which the stomach contents are ejected along the oesophagus into the mouth during expiration. Contraction of the muscles that elevate the soft palate prevents vomit from entering the nose, while the larynx is protected by respiration being suppressed and the root of the tongue being pulled downwards; the mouth opens widely.

The afferent nerve fibres responsible for vomiting form part of n. vagus, n. glossopharyngeus, and certain other nerves. They conduct excitation to a vomiting nerve centre located in the medulla oblongata on the floor of the fourth ventricle. The efferent nerves that excite it are the vagus and sympathetic splanchnic nerves to the intestine, stomach, and oesophagus, and also those that innervate the abdominal muscles and the diaphragm. Vomiting cannot occur if the vagus and sympathetic nerves are cut (although separate components of the act may be retained).

#### DIGESTION IN THE DUODENUM

Food entering the duodenum is exposed to the action of pancreatic juice, bile, and the juices secreted by Brunner's and Lieberkühn's glands lying in the duodenal mucosa.

In the absence of digestion the duodenal contents are weakly alkaline (pH averages 7.2 to 8.0). With the entry of a portion of the acid contents of the stomach into the duodenum its contents also become acid, but alkalinity is soon restored as the hydrochloric

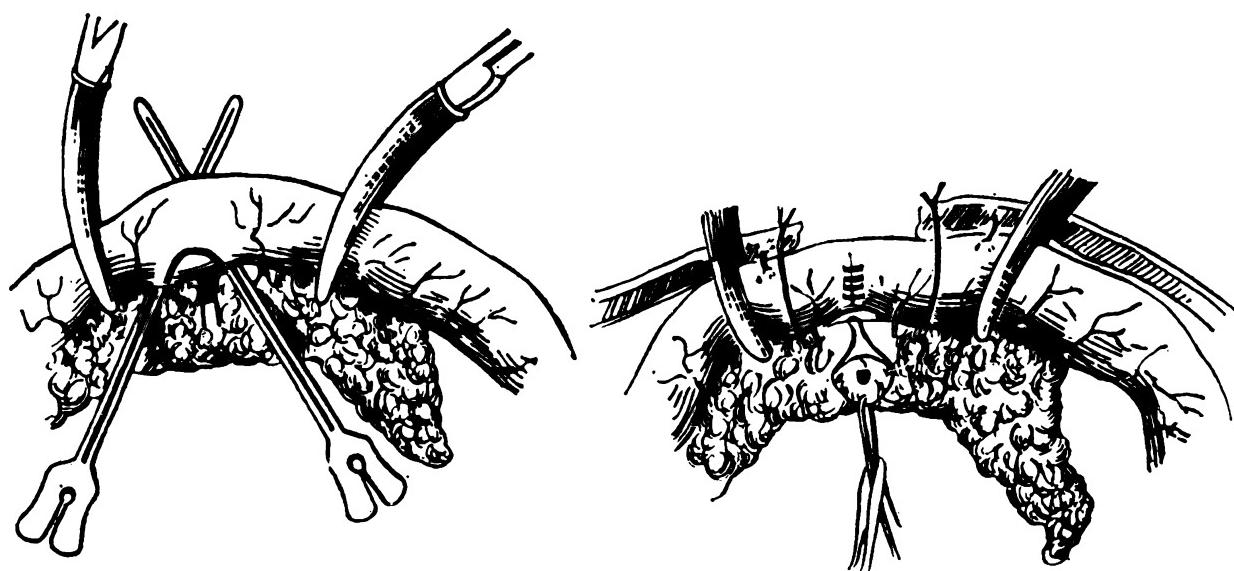


FIG. 83. Two stages of operation for creation of a pancreatic fistula

acid of gastric juice is neutralized. The pH of duodenal contents varies in man between 4.0 and 8.5.

#### METHODS EMPLOYED TO STUDY PANCREATIC SECRETION

Pancreatic secretion is studied in animals by acute and chronic experiments. The latter are conducted through a fistula of the pancreatic duct, created as follows by Pavlov's technique. The portion of the duodenal wall containing the opening of the duct is excised, integrity of the intestine is restored by suturing, while the mobilized portion is stitched into a skin wound (Fig. 83). After the animal has recovered from the operation, the experimenter can observe pancreatic secretion for many months.

The collection and examination of pure pancreatic juice in man is impossible under normal physiological circumstances. Duodenal catheterization yields contents that always include bile and gastric juice as well as pancreatic secretion. Individual cases, however, of a fistula of the pancreatic duct have been described.

#### THE COMPOSITION AND PROPERTIES OF PANCREATIC JUICE

The juice secreted by the pancreas is a transparent, colourless fluid which is alkaline, because of the presence of bicarbonates. Human pancreatic juice has a pH between 7.8 and 8.4.

Pancreatic juice is rich in enzymes. It contains: *trypsin* and *chymotrypsin*, which act upon proteins; *carboxy polypeptidase* and *aminopeptidase*, which split polypeptides; *lipase*, which hydrolyses fats; *amylase*, which breaks starch down to disaccharides; *maltase*, which converts disaccharide maltose into monosaccharide glucose; *lactase*, which breaks milk sugar, lactose, down to monosaccharides; and *nucleases*, which act on nucleic acids.

Pancreatic juice collected from the pancreatic duct has no effect on proteins because it contains inactive forms of trypsin and chymotrypsin known as *trypsinogen* and *chymotrypsinogen*. The addition of small quantities of gastric juice converts trypsinogen into the active enzyme trypsin, due, it is thought, to the effect of a peculiar enzyme *enterokinase* present in gastric juice and discovered in Pavlov's laboratory in 1899 by Shepovalnikov. Under the action of enterokinase, which Pavlov called "the enzyme of an enzyme", a peptide consisting of six amino acids is split off from trypsinogen, which then becomes active. The peptide evidently neutralizes trypsin. After its own activation, trypsin in turn activates chymotrypsinogen.

Through action of trypsin and chymotrypsin in an alkaline medium, proteins and their breakdown products, high-molecular polypeptides, are broken down to low-molecular peptides and amino acids. Tryptic protein digestion continues and supplements the peptic digestion that occurred in the stomach. (The action of pepsin is arrested in the duodenum by its alkaline content and by bile.) The action of trypsin is maximum in a weakly alkaline medium.

The carboxy-polypeptidase present in pancreatic juice also breaks down complex polypeptides.

The pancreatic lipase breaks fats down into glycerin and fatty acids; its influence is greatly intensified by bile.

#### SECRETION OF PANCREATIC JUICE IN RESPONSE TO VARIOUS FOODSTUFFS

Pancreatic secretion begins two to three minutes after a meal and lasts for six to fourteen hours, depending on the composition of the food. When digestion is not taking place, i. e. on a fasting stomach, secretion occurs from time to time due to the hunger activity of the gastro-intestinal tract (p.275). The quantity of juice and its enzyme composition depend on the type of food eaten.

A characteristic secretion is observed after consumption of meat, bread, or milk which reaches a maximum during the second hour in response to meat, during the first hour in response to bread, and during the third hour in response to milk.

The quantity of juice produced in man after a meal of meat containing little fat is 150 per cent of that excreted after foods rich in fat. Eating fatty foods over a long period leads to a gradual, day by day, decline in pancreatic secretion.

Experiments on animals have shown that the enzyme composition of pancreatic juice alters with the character of the food. Similar data has been obtained from observations of human subjects. The amount of lipase increases with a diet rich in fats, the quantity

of amylase with a carbohydrate diet, and the amount of trypsin with a meat diet.

When compared, the curves of pancreatic and gastric secretion are found to be similar, which indicates that the function of these glands are closely related.

Pancreatic secretion, like that of other glands, results from the activity of secretory cells and is attended with expenditure of energy and heightened oxidation processes. The uptake of oxygen by a working gland increases by 100 to 200 per cent and the temperature of its tissue rises.

#### CONTROL OF PANCREATIC SECRETION

Two types of mechanism regulate pancreatic secretion, the neural and the humoral.

Pavlov demonstrated, in both chronic and acute experiments, that the *vagus nerve* is the *secretory nerve of the pancreas*.

In chronic experiments conducted on a dog with a pancreatic fistula one of the vagus nerves was cut at the neck and its peripheral end fixed under the skin. Four or five days later, when degeneration of the nerve had already begun, electrical stimulation excited secretion. The vagus nerve carries fibres that stimulate secretion and others that inhibit it. The latter degenerate more rapidly, so that stimulation of them several days after cutting of the nerve does not interfere with the effect of the fibres that cause secretion. Stimulation of the other vagus nerve arrested secretion owing to dominance of the effect caused by stimulating the inhibiting fibres. The flow of pancreatic juice can also be arrested by stimulating other nerves, for example, the sensory nerves of the skin; the inhibition in that case occurs through reflex pathways.

Vagal stimulation excites secretion of a small quantity of juice with high enzyme activity.

The existence of a reflex mechanism has been demonstrated in chronic experiments on complexly treated animals (Tonkikh). Secretion is excited, on the one hand, by the sight and smell of food and by various other stimuli associated with a meal (conditioned reflex stimuli) and, on the other hand, by the chewing and swallowing of food (unconditioned reflex stimuli). The act of eating, which stimulates receptors in the mouth and pharynx, is a powerful stimulus of reflex pancreatic secretion. The nerve impulses originating in these receptors reach the nerve centre of pancreatic secretion in the medulla oblongata, pass along the vagal fibres to the gland, and excite its activity.

As already mentioned, the pancreas begins to secrete juice a few minutes after food is eaten. This short latent period is an indicator of the reflex character of the process. In an individual with a fistula of the pancreatic duct it was found to occur a few minutes after

being told about the meal he was to receive, a case of secretion being induced by a conditioned reflex.

The entry of hydrochloric acid solutions or gastric juice into the duodenum acts as a powerful stimulus of pancreatic secretion. Bayliss and Starling established that hydrochloric acid has an effect on the cells of the duodenal mucosa, evoking production of a substance called *secretin* which is carried to the pancreatic cells by the blood stream and excites their activity.

That is confirmed by the fact that the introduction of hydrochloric acid extracts of duodenal mucosa into the blood stimulates the flow of juice. The active substance responsible is a specific chemical stimulator, or hormone, produced in the duodenal mucosa. Secretin is formed in the duodenum under the influence of gastric hydrochloric acid from an inactive substance, *pro-secretin*, secreted by the cells of the mucosa.

Thus, pancreatic secretion is under both *nervous* and *humoral control*. The existence of the latter has also been demonstrated in experiments in which the pancreas was removed from the abdomen and transplanted under the skin with the duct stitched to the skin wound. Although the transplanted gland had no nerve connections with other organs and was linked with the body only by the circulation, it continued to secrete juice at definite stages of digestion.

Further, the humoral mechanism has been studied in experiments with cross-circulation. The blood vessels of two dogs were so connected that the blood of one entered the vessels of the other. Pancreatic secretion was observed in both dogs on the introduction of hydrochloric acid into the duodenum of one of them.

Hydrochloric acid causes the formation of secretin only in the upper segments of the small intestine, mainly in the duodenum, because the mucosa of the lower segments is devoid of pro-secretin.

The activation of pro-secretin and its conversion to secretin, occurs under the influence of inorganic acids and of most organic ones. It is caused by the salts of fatty acids (soaps). A crystalline hydrochloride salt of secretin has been derived from extracts of duodenal mucosa; it has been established that secretin is a polypeptide with a molecular weight between 3,200 and 3,500.

It is assumed that two active substances affecting two different functions of the pancreas are formed in the duodenal mucosa, viz. *excretin* which influences its external secretion, i.e. the secretion of its digestive juice (excretin is identical with the secretin discovered by Bayliss and Starling); and *incretin* which is concerned with internal secretion, i.e. with secretion of the hormone insulin into the blood.

An extract has been obtained from the mucosa of the small intestine which, when introduced into an animal, induces secretion of pancreatic juice rich in enzymes. The extract has been shown to contain, in addition to secretin, which has no enzyme-producing

effect on the cell, a substance, *pancreozymin*, which stimulates the production of enzymes.

The pancreatic juice secreted in response to introduction of secretin contains inactive trypsinogen, which is converted to trypsin under the influence of the enterokinase of gastric juice, while vagal stimulation induces production of active trypsin capable of protein digestion without previous activation by enterokinase.

#### THE SECRETION AND PLACE OF BILE IN DIGESTION

Bile is a product of the secretory activity of liver cells. Its role in digestive processes is various and consists in the following: bile activates the enzymes produced by the pancreas and gastric glands (its activating effect being especially pronounced in the case of lactase, which brings about the breakdown of about twenty times as much fat when bile is added to the solution); bile emulsifies fats and in that way facilitates their splitting and absorption; bile stimulates intestinal movements, and on entering the intestine brings about pancreatic secretion.

All these facts illustrate the importance of bile in digestion, particularly in the digestion of fats. The daily volume secreted in man varies between 500 and 1,000 millilitres. Any impairment in its supply to the intestine leads to deficient assimilation of fats.

Bile is secreted continuously by the cells of the liver, but its ejection from the common bile duct into the intestine occurs only after food enters the stomach and intestine. In the absence of digestion it is accumulated in the gall bladder.

Bile discharged from the hepatic duct differs in composition and properties from that stored in the gall bladder; the former is an easily flowing transparent fluid, light-yellow in colour, while the latter is darker, almost black, much thicker, and rich in solid substances owing to an admixture of mucus secreted by the gall-bladder mucosa and the absorption of some of its water by the gall-bladder wall during storage. Its concentration increases by seven to ten times over 22 to 24 hours.

Specific organic substances that are constituents of bile are *bile acids* and *bile pigments*.

Bile also contains lecithin, cholesterol, fats and soaps, mucin which is secreted by the mucous membrane of the bile ducts and gall-bladder, and inorganic salts, but no enzymes.

Although bile is weakly alkaline in reaction, it contains two acids, *glycocholic* and *glycocholic*, which are formed in the liver. Convincing evidence of that is yielded by experiments involving extirpation of the liver. Slight quantities of bile can always be found in the blood; bile acids disappear from the blood of animals whose

liver has been removed, but with ligation of the bile duct their content in the blood increases sharply.

The bile pigments are *bilirubin* and *biliverdin*, the latter being a product of bilirubin oxidation. Bilirubin predominates in human bile. It is formed from haemoglobin liberated in the destruction of erythrocytes. One gramme of haemoglobin produces 40 milligrams of bilirubin.

The site of pigment production was established by resection of the liver in animals. The dogs used survived the operation for more than 24 hours. The experiments demonstrated that the bilirubin content of blood did not fall after removal of the liver but even tended to rise three to six hours after surgery, and showed a marked increase if haemolysed blood was injected intravenously. This leads to the conclusion that the liver is not the only site of bilirubin production in dogs but that the pigment is also produced in other organs (namely, in the bone marrow, spleen, and lymph nodes). In all probability bile pigments are produced in the cells of the reticulo-endothelial system.

That bilirubin is produced by the reticulo-endothelial cells is confirmed in experiments in which this tissue is cultivated outside of the body. Erythrocytes introduced into it are destroyed and bile pigments produced.

Certain substances stimulate bile secretion in the liver via humoral pathways. They include gastrin, duodenal secretin, and meat extracts, which all excite bile production by acting directly upon the secretory cells.

Bile itself is a peculiar humoral stimulator of its own secretion. When introduced into the blood, it excites secretory activity of the hepatic cells, which produce a quantity of bile much larger than that injected into the blood.

#### BILE EJECTION

The secretion and ejection of bile is studied in acute and chronic experiments on animals. Chronic experiments are conducted in two ways: 1) by establishing a fistula of the gall-bladder, and 2) by bringing the opening of the common bile duct out to the skin surface together with part of the surrounding duodenal mucosa. The first method is used to study secretion by the cells of the liver and the mechanism of bile production. To prevent bile entering the duodenum, and to collect all the bile continuously secreted by the hepatic cells, the common bile duct is frequently ligated in addition to creating a fistula of the gall-bladder. Then all the bile secreted accumulates in the bladder and can be collected from the fistula and studied. The second method allows the conditions and mechanism of the evacuation of the bile into the intestine to be examined.

Research using both methods simultaneously yields a complete picture.

In man bile secretion is studied by X-rays by introducing radio-opaque substances (bilitrast or bilignost) that are eliminated in the bile. A shadow is seen on the X-ray screen around the bile ducts and gall-bladder after injection of those substances into the blood, and the flow of bile can be watched.

Bile enters the duodenum within a short time (five or ten minutes) after a meal, and its excretion curve varies with the foods eaten. Its flow ceases as soon as the last bit of food leaves the stomach. The first portions of bile emptied into the duodenum are dark, which shows that they come from the gall-bladder; later portions are lighter in colour and are hepatic bile.

Bile ejection is due to co-ordinated activity of the gall-bladder and of the sphincter of the common bile duct which lies at its opening into the duodenum and regulates the flow of bile into the intestine. Their action is controlled by two mechanisms, one reflex and the other humoral. The reflex mechanism is caused by unconditioned reflexes, i. e. by the entry of food into the stomach and duodenum, and by conditioned reflexes (the sight and mention of food). One of the stimuli exciting reflex contraction of the gall-bladder is mechanical stimulation of the gastric mucosa.

The influence of the nervous system on bile apparatus is effected through the vagus and sympathetic nerves. The opening and closing of the duct sphincter, and the contraction or relaxation of the gall-bladder, occur through impulses conducted along these nerves. Weak stimulation of the vagus nerve relaxes the sphincter, while the application of a strong stimulus causes it to contract; as a rule, contraction of the sphincter is attended with relaxation of the gall-bladder, and vice versa. Owing to this co-ordinated activity bile accumulates in the gall-bladder in the absence of digestion, and enters the duodenum after food is eaten or during the hunger activity of the alimentary tract (p. 275).

The presence of humoral stimulators in the blood has been proved on experimental animals. A flow of bile is excited in a fasting animal when blood taken from another animal at the peak of digestion is injected into its blood stream. The transfusion of blood collected during a fasting state has no such effect.

Ivy discovered that a peculiar chemical stimulator of gall-bladder activity, *cholecystokinin*, is formed by the duodenal mucosa under the influence of hydrochloric acid, fatty acids, and certain other substances. It intensifies the contractions of the bladder and causes its evacuation at the peak of digestion.

Cholecystokinin preparations are extremely potent, exciting marked contraction of the gall-bladder if introduced in amounts less than 0.2 of a milligram. They are used in clinical practice.

### GLANDS OF THE DUODENAL MUCOSA

The mucous membrane of the duodenum lodges a great number of Brunner's glands in its upper segments, and of crypts of Lieberkühn along its entire length.

The *Brunner's glands* resemble the pyloric glands in structure and, possibly, in function. The juice secreted by them is a thick, colourless, alkaline fluid containing much mucus and a protein enzyme that is similar to pepsin and active in an acid medium. The juice has a weak fat- and starch-splitting effect, and activates the enzyme of the pancreatic secretions. Owing to its properties, the juice secreted by Brunner's glands appears to be transitional between that produced by the pylorus and by the crypts of Lieberkühn.

### DIGESTION IN THE SMALL INTESTINE SECRETION BY THE INTESTINAL GLANDS

The mucous membrane of the small intestine contains *crypts of Lieberkühn* (or *Lieberkühn's glands*) along its entire length, which secrete enteric juice.

*Enteric juice* is an alkaline, colourless fluid, slightly cloudy owing to an admixture of mucus, epithelial cells, and cholesterol crystals, and contains sodium chloride and a small amount of carbonates. It enters into the digestion of foods in the duodenum.

In addition to enterokinase, which converts trypsinogen to trypsin, enteric juice contains enzymes that act upon carbohydrates, fats, and products of protein digestion formed in the stomach and duodenum. These products are broken down to amino acids by a mixture of *peptidases* (*aminopolypeptidase*, *dipeptidase*, etc.), i. e. a complex of proteolytic enzymes previously known as erepsin. The enzyme *nuclease*, which acts upon the nucleic acids, is present in enteric juice; *lipase* and *amylase*, characterized by low activity, can also be found in it. In the small intestine disaccharides are broken down by the action of enzymes also present in its secretions, viz. malt sugar by *maltase*, cane sugar by *invertase*, and milk sugar by *lactase*.

Thiry proposed surgical isolation of an intestinal loop in order to study the secretory function of the small intestine in chronic experiments. A segment of the intestine is resected without injuring the mesentery and its blood and lymphatic vessels and nerves; one end is completely sutured, while the other is stitched into the skin wound, and continuity of the intestine is restored by suturing the divided upper and lower portions. Vella modified the operation by suggesting that both ends of the loop be brought to the outside (Fig. 84).

There is a view that the enteric secretion of enzymes differs in character from that in other digestive glands. On secreting digestive

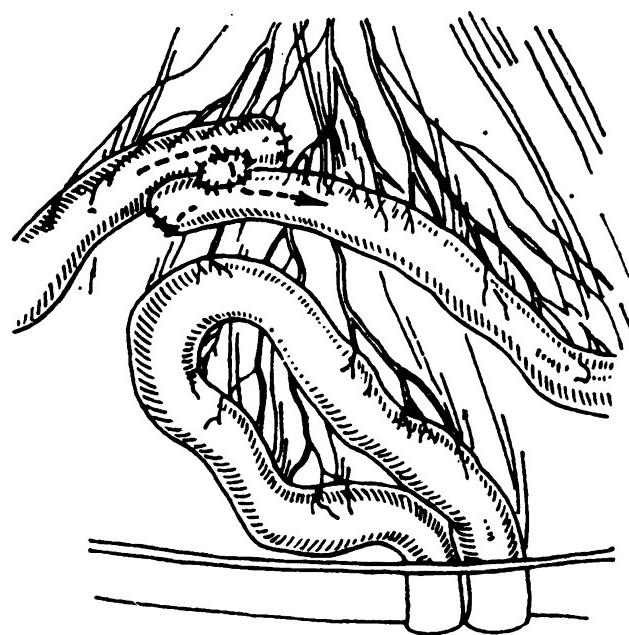


FIG. 84. Isolated intestinal loop  
created after Thiry-Vella

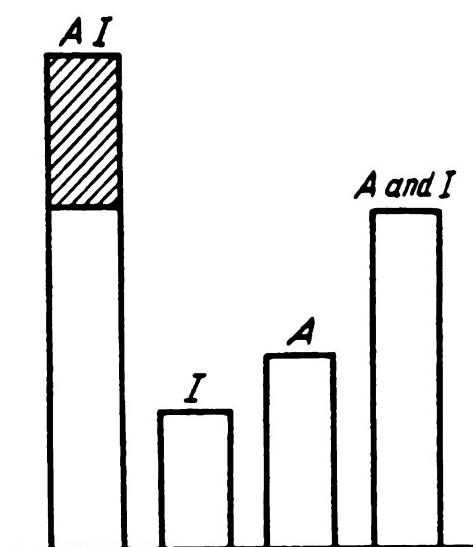
juices, the cells of the salivary, gastric, and duodenal glands remain intact (*morphostatic secretion*), but the discharge of enzymes in enteric juice is attended by destruction of the gland cells (*morphecrotic secretion*). The surface epithelial layer of the intestinal mucosa is continuously being replaced. On the one hand, new cells are formed abundantly by division, and, on the other hand, destroyed cells are continuously discarded with the formation and discharge into the intestinal lumen of mucous clots rich in enzymes. With this type of secretion, the enzymes are not so much excreted by the cell as liberated on disintegration of dying cells (Shlygin).

Mechanical stimuli and certain chemical ones increase the flow of enteric juice when applied directly to the intestinal mucosa.

The effect of mechanical stimulation can be observed if beads, peas, or a rubber catheter are introduced into the isolated intestinal loop. The chemical stimuli include gastric juice, products of protein digestion, soaps, milk sugar, etc. Their secretion-stimulating action persists after cutting of the nerves supplying the intestine (nn. vagi and nn. splanchnici).

It has been supposed that secretion from the intestinal glands in response to mechanical or local chemical stimulation is caused by a peripheral reflex effected by nerve cells of the plexuses lying in the intestinal wall, but influence of the central nervous system on the secretion of enteric juice has not been proved.

Activity of the intestinal glands can be stimulated by introducing duodenal mucosa extracts treated in a certain way into the blood flow. Nasset showed that the same effect can be obtained by a particular hormone, *enterocrinin*, not identical with secretin, that is formed in the intestinal mucosa.



**FIG. 85.** Rate of starch hydrolysis: by dissolved amylase (*A*); by amylase adsorbed on the intestine (*I*); and by the combined effect of dissolved and adsorbed amylase (*AI*). The effect produced in the latter case is much greater than the sum of *A* and *I* (after A. M. Ugolev)

#### MEMBRANE (CONTACT) DIGESTION

Research into the digestive processes in the small intestine has revealed the importance of contact between food and the mucosa. Experiments in test tubes have shown that the rate of enzyme hydrolysis of certain nutrients, for example, starch, increases in the presence of a strip of live intestine, the activity of the process greatly exceeding the sum of the separate activities of the enzyme-containing solution and of the intestinal strip (Fig. 85). Ugolev shows from experimental data, that the extensive porous surface of the small intestine helps to intensify enzyme processes by adsorbing the enzymes and serving as a kind of porous catalyst. It is important to note that according to his data, the final breakdown of nutrients takes place on that adsorbing surface (p.267). This breakdown of nutrients on the intestinal surface is known as *membrane digestion*, as distinct from that taking place in the cavity of the alimentary canal without direct contact with the mucosa.

#### MOTOR FUNCTION OF THE SMALL INTESTINE

The movements of the small intestine result from co-ordinated contractions of longitudinal and circular muscular fibres. Two types of intestinal movement are distinguished — pendular and peristaltic.

The *pendular movements* consist in an alternate shortening and lengthening of small segments of the intestine by which its contents are moved first in one direction and then in another. The movement is caused by alternate rhythmical contractions of the longitudinal and circular muscle fibres of the intestine. Contraction of the longitudinal musculature shortens and, consequently, dilates a segment. Contraction of the circular musculature narrows the lumen and pushes the contents away from the constricted segment in both directions. Contractions occur without any order, now in one part of the intestine, and now in another. Their rhythm reaches

twenty per minute in the upper segments and five to ten per minute in the lower ones. These asynchronous contractions give rise to what is called *rhythical segmentation* by which food is divided (segmented) and then mixed together again and again.

The physiological role of pendular movements is their mixing of food with the digestive juices.

With the other type of intestinal movement *peristalsis*, a circular constriction forms above a bolus of food owing to contraction of the circular muscles, while the lumen below the bolus is dilatated by contraction of the longitudinal muscles. As a result, the intestinal contents move toward the widened part; then contraction of the circular muscles spreads to this part which in turn is constricted, while the segment lying below it is distended by contraction of the longitudinal musculature.

Thus, a wave of circular-muscle contractions spreads from segment to segment along the intestine, preceded in each segment by contraction of the longitudinal muscles in the adjoining lower one. Naturally, this type of movement propels the contents of the intestine in one direction only—downward.

Several of these wave-like contractions occur simultaneously along the length of the intestine, so that its movement is vermiform. Hence they are called vermicular or peristaltic movements.

Both rhythmical contractions, pendular and peristaltic, occur against a background of a persisting *tone*, or certain tension of the intestinal muscles, which is not constant in character and may increase or decrease.

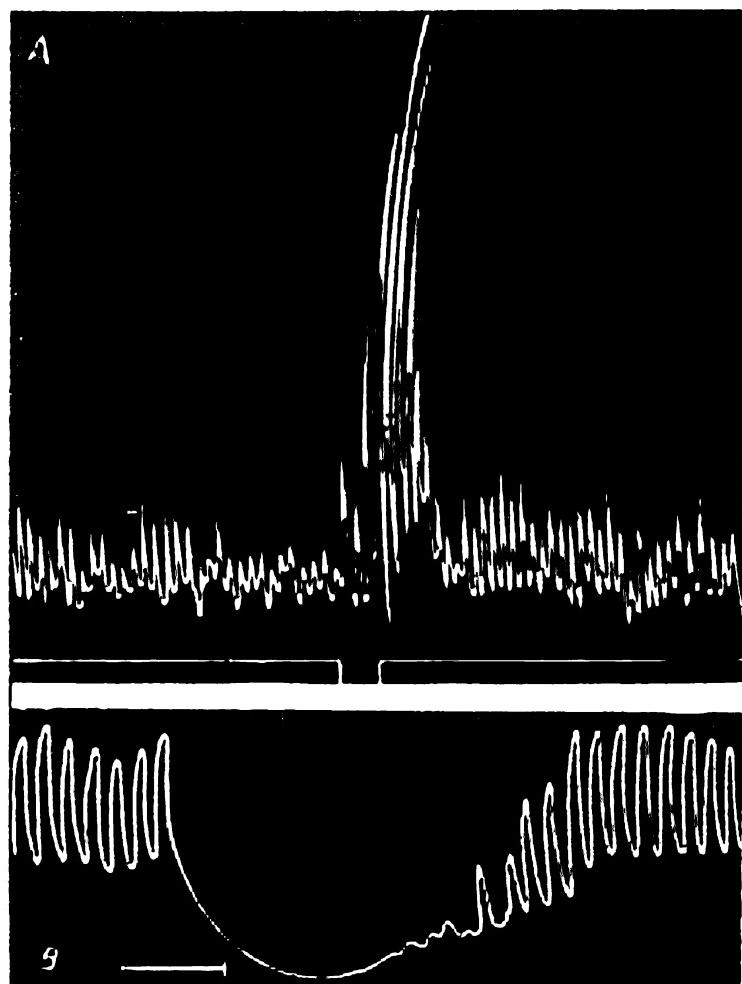
The smooth muscle fibres of the intestine possess automatism, which is exhibited by their ability to contract rhythmically without being stimulated by external stimuli.

This automatism, and the effect produced on the musculature by various salts, poisons, and other substances, can be studied in an isolated intestinal loop removed from the body. The loop continues to contract for hours when suspended in Locke's or Tyrode's solution warmed to body temperature and saturated with oxygen.

The muscles of the intestine, like those of the stomach, maintain their rhythmical pendular contractions after removal of the ganglion cells that form the Auerbach plexus, which is grounds for assuming that the rhythmical automatism is of myogenic origin, i. e. is characteristic of the muscular elements.

As for peristaltic movements, which are a quite complex, co-ordinated type of activity, it has been found that they are encountered only when there are nerve cells of the Auerbach plexus, which are responsible for the co-ordinated contraction of the longitudinal and circular muscles in the intestinal wall.

The activity of the intestinal muscles is under both reflex and humoral-chemical control. Impulses from the central nervous system reach them along the vagus and sympathetic nerves. The char-



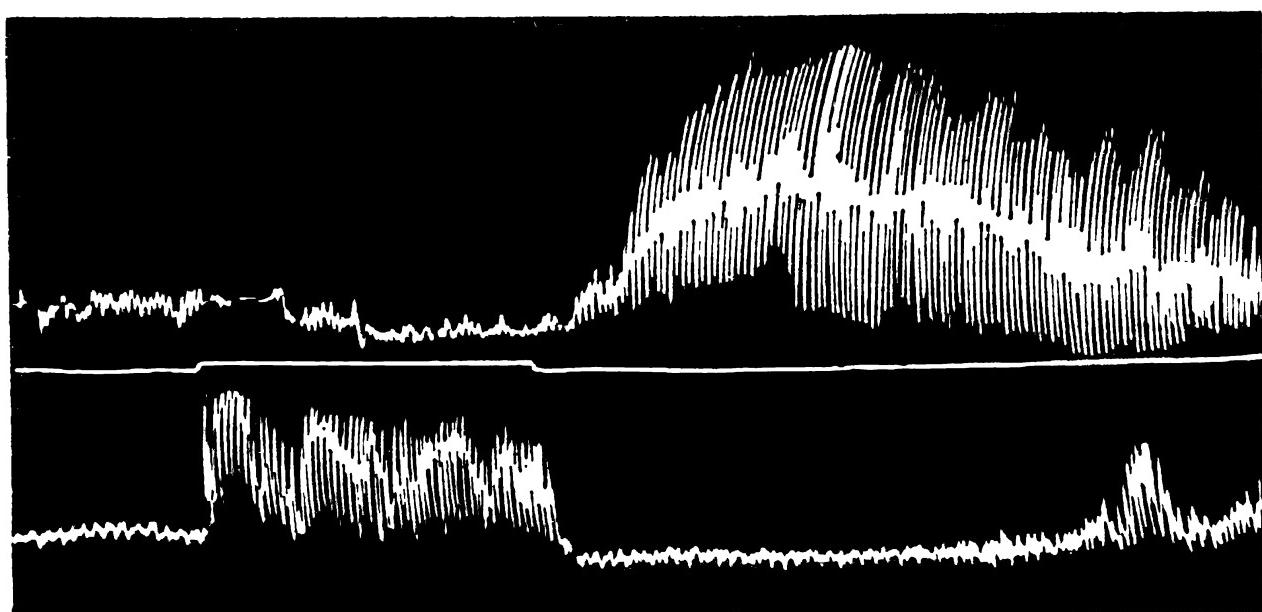
**FIG. 86. The effect of vagal (A) and sympathetic (B) stimulation on the motility of the small intestine**

acter of the influence exerted by these nerves on intestinal movement is opposite in effect; it can be studied experimentally by electrical stimulation. Stimulation of nn. vagi excites intestinal movement, i. e. intensifies muscular contraction and raises tone (Fig. 86 A). Stimulation of n. splanchnicus inhibits intestinal contraction and causes a sharp decrease in the muscular tone (Fig. 86 B). The nerves innervating the intestine, however, may produce effects different from those described here, depending upon the strength of the stimulation, state of the intestinal muscles, blood chemism, character of metabolic processes, and other physiological factors.

The influence of the nervous system on intestinal motor function is clearly seen in man or animal in emotional states. Anger, fear, and pain usually inhibit contractions because the sympathetic nervous system is excited. Certain strong emotions, like fear, may sometimes cause extremely active peristalsis ("nervous flux").

When the vegetative nerves supplying the intestine are stimulated, chemical transmitters of the nerve impulse, or *mediators*, form in their endings—acetylcholine in the vagus nerve endings, and noradrenaline in the sympathetic nerve endings.

If breakdown of acetylcholine by cholinesterase is prevented in one of the two dogs connected by cross-circulation, then stimulation



**FIG. 87.** The influence of vagal stimulation on the motility of the small intestine in two dogs under conditions of cross-circulation (after E. Babsky et al.)

The middle line shows the period of vagal stimulation in one of the dogs. Once the stimulation of the vagus nerve in this dog ceases (lower tracings) marked intestinal contractions occur in the other (upper tracings)

of its vagus nerve is accompanied by changes in intestinal contraction in the other dog (Fig. 87). This occurs because the acetylcholine not destroyed by cholinesterase enters the blood and can produce an effect at a distance from the organ where it is formed.

Choline and certain other substances, like enterocrinin (p.257) and 5-hydroxytryptamine (serotonin), formed by the mucous membrane of the duodenum and small intestine, which enter the blood during digestion, are humoral stimuli that excite intestinal motility. They are considered to be specific hormones and stimulators of intestinal movement. Polypeptides, extractive substances, bile, and potassium, calcium, and magnesium salts, which are absorbed in the intestine also influence its motor activity via humoral pathways.

The smooth muscles of the intestine contract through mechanical and chemical stimulation of the mucosa. Thus, distention of the intestinal wall by the partially digested food (*chyme*) coming from the stomach excites peristaltic and pendular movements. The more rapidly distention occurs, the more actively the muscles contract. The fact that "roughage", consisting of not very digestible substances, like bran, is a potent stimulus of intestinal movement, is attributed to mechanical stimulation.

Acids, alkalis, and many salts (in concentrated solution), which evoke intestinal movements on coming in contact with the mucosa, are chemical stimuli. The introduction of gastric acid, for instance, or of weak acid or alkaline solutions, into the intestine markedly

intensifies its contraction and increases muscular tone. Certain digestion products, like soaps, excite sharp movements of the alimentary tract.

The mechanism responsible for the action of all local mechanical and chemical stimuli, i. e. those that act on the intestinal mucosa, is quite complex. First, they may exert a reflex influence through stimulation of the mucosal mechano- and chemoreceptors, and second, they may stimulate the formation of chemical substances that excite intestinal movement on being absorbed into the blood.

### DIGESTION IN THE LARGE INTESTINE

#### PASSAGE OF INTESTINAL CONTENTS INTO THE LARGE INTESTINE

Food that has not been absorbed in the small intestine enters the initial portion of the large intestine, or caecum, through the *ileocaecal sphincter*, which has a complex structure and acts as a valve permitting passage only in one direction (the contents of the large intestine cannot return to the small intestine). The structure of the sphincter is such that it closes tightly as soon as the caecum is distended by inflowing contents, and does not allow their return.

The ileocaecal sphincter remains closed when digestion is not taking place. One to four minutes after a meal it begins to open rhythmically every 30 to 60 seconds and small portions of chyme (up to 15 millilitres) pass into the caecum from the small intestine. Its opening after intake of food results from a reflex arising in the stomach (the viscero-visceral reflex, see Vol.II, Chapter 16 on vegetative innervation of tissues and organs).

#### CHANGES OCCURRING IN THE LARGE INTESTINE

The large intestine or colon is only slightly involved in digestive processes as such since food is almost completely digested and absorbed in the small intestine, with the exception of certain substances like vegetable cellulose tissue.

In experiments made by London, a dog was fed its entire daily ration of food in one meal. Only 10 per cent of the ingested nitrogenous substances (made up of nitrogen-containing, or protein food particles and digestive juices not absorbed in the small intestine), 5 per cent of the starch, and 3 per cent of the fats entered the large intestine, while 7 per cent of the nitrogen, 3 per cent of the carbohydrates, and 3 per cent of the fats were found in the faeces. Thus, only small quantities of protein and carbohydrate are digested and absorbed in the colon. Digestion occurs through the action of enzymes secreted by the upper portions of the alimentary tract.

The large intestine contains a rich bacterial flora which effects carbohydrate fermentation and protein decay. Bacterial ferment-

tation breaks down vegetable cellulose tissue, which is not assimilated in the small intestine and enters the large intestine unchanged since the digestive juices do not act upon it. Its breakdown releases vegetable cells which are then split by the action of the enzymes in enteric juice and partly absorbed.

Unabsorbed amino acids and other products of protein digestion are destroyed in the colon by the action of putrefactive bacteria; in the process a number of toxic compounds (indole, skatole, phenol, etc.) are formed that are capable of causing intoxication if absorbed by the blood. They are detoxified in the liver.

The contents of the large intestine are thickened through absorption of water, and faeces of a solid consistency are formed. The solid material in the intestinal juice, namely, clumps of mucus, play an important role in the formation of the faecal mass by binding together the particles of undigested food remains.

The constituents of faeces are as follows: mucus, the remnants of destroyed mucosal epithelium, cholesterol, breakdown products of bile pigments (which are responsible for the characteristic colour of faeces), insoluble salts, and bacteria (which account for 30 to 40 per cent of the daily faecal discharge). The faecal mass also contains undigested food remains like cellulose, keratins, and certain collagens; various amounts of protein, fat, and carbohydrate may be found in it in disorders of the digestive processes and impairment of absorption.

#### THE MOVEMENTS OF THE LARGE INTESTINE

With a diet consisting of animal and mixed foodstuffs, the whole digestive process lasts between one and two days, the propulsion of food remains along the large intestine accounting for more than half of that time. Research using radiopills has shown that food may stay in the caecum for hours, moving slightly first in one direction and then in another; with a large intestine filled with a barium meal very slow peristaltic and pendular contractions are seen by X-ray (Fig. 88).

The large intestine possesses automatism, but it is weaker than that of the small intestine.

The caecum and the ascending and transverse portions of the colon are supplied with parasympathetic fibres by the vagus nerve. The other parts of the large intestine have parasympathetic motor fibres from the sacral spinal segments. In addition, it is innervated by sympathetic fibres arising mainly from the inferior mesenteric plexus, but also from the superior.

It has been demonstrated by means of an isolated colon loop created surgically by Gubar's method, that movement of the large intestine is excited mainly by mechanical stimulation of its mucosa.

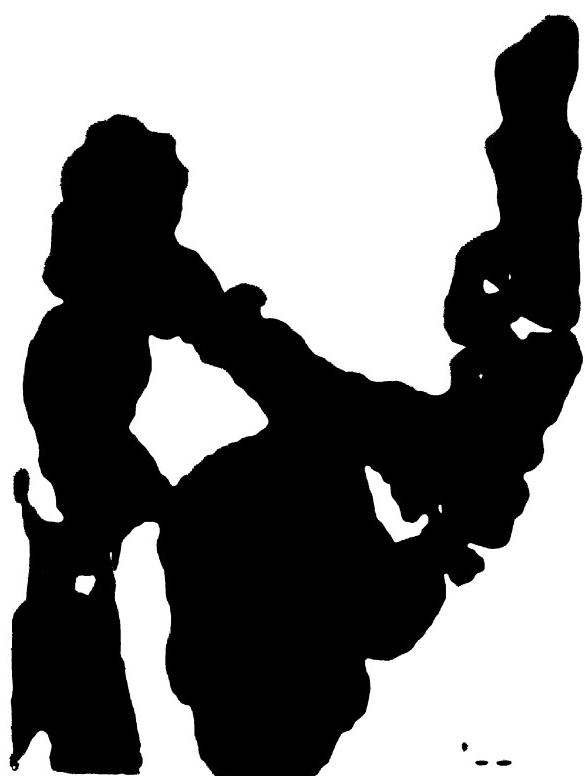


FIG. 88. X-ray of the large intestine filled with a barium meal

#### DEFAECATION

The rectal sphincters, the internal consisting of smooth muscle fibres, and the external formed by striated muscles, are in a state of continuous tonic contraction. *Defaecation*, i. e. the evacuation of the large intestine and discharge of faeces, occurs through stimulation of the sensory nerves of the rectal mucosa by the faecal masses accumulated in the rectum. Reflex relaxation of both sphincters opens the exit from the rectum, and the faeces are expelled by peristaltic movements of colon and rectum. This is facilitated by contractions of the abdominal muscles and diaphragm effected by straining, and also by contraction of the levator ani muscles that pull up the rectal sphincter. Contraction of the abdominal muscles causes a marked increase in intra-abdominal pressure.

The centre of the defaecation reflex lies in the lumbar division of the spinal cord. Cutting of the cord below that centre, or destruction of the centre itself results in a gaping anus due to relaxation of the sphincters, and retention of faeces becomes impossible; but the tone of the sphincters is partly restored some time after under the influence of the peripheral nervous system.

If the spinal cord is cut above the centre, the act of defaecation persists but becomes involuntary. Voluntary control is effected from the cerebral cortex, apparently from the anterior central gyrus. Involuntary relaxation of the sphincters and defaecation may occur with certain emotions, like fear.

Motor nerve fibres run to the rectal sphincters from the anterior sacral roots of the spinal cord in the parasympathetic pelvic nerve.

Sympathetic fibres reach them through the anterior roots of the lumbar segments and the inferior mesenteric ganglion.

### ABSORPTION

The penetration of various substances from the external environment, body cavities, or hollow organs, into the blood or lymph through the one or more layers of cells that form the complex biological membranes is known as *absorption*. These biological membranes include the epithelial layer of the skin, the mucosa of the intestine, gall-bladder, pulmonary alveoli, the endothelium lining the serous coats of the peritoneal cavity, pleural space and joint capsules, the endothelial layer of the capillaries, the brush-border epithelium of the renal tubules, etc. All biological membranes, both those covering a single cell, and the complex ones consisting of several layers of cells, are *semi-permeable*. That means that they allow the passage of certain substances but not of others. Cell membranes are mainly permeable to substances that form true solutions and impermeable to those that occur in a colloidal state, and permit many substances to pass only in one direction.

Various solutions can be absorbed from the surface of the skin. Human skin is not very permeable to most organic and inorganic substances. Many substances that occur as gases or are sprayed in the air can penetrate the surface of the pulmonary alveoli. Vapours of chloroform, ether, and certain war gases inhaled with the air gain entrance to the blood in that way. A number of substances injected into the subcutaneous cellular tissue, or into the abdominal cavity, pleural space, or cerebrospinal canal, can also be absorbed, i. e. may enter the blood or lymph stream.

The absorption occurring in the alimentary canal is of special physiological importance since it is through it that the body is supplied with the nutrients it requires.

### THE USE OF ISOTOPES TO STUDY ABSORPTION

The absorption of substances not encountered in the body under normal physiological conditions, as for example, various toxins, can be established fairly easily either by revealing phenomena characteristic of their effect or by detecting their presence in the blood. It is much more difficult to study the absorption of substances that are always present in the body (such as amino acids, glucose, fats, sodium, potassium and calcium salts, water, etc.), or of those that undergo rapid chemical changes and circulate in the blood stream for only a short time. The use of labelled compounds has made it possible to overcome many of the methodological difficulties encountered in research. The label that permits the studied substance to be distinguished from others occurring in the organism is an isotope

of one of the constituent elements, a substance which is introduced into it. The isotope of an element differs from its commonly encountered form in atomic weight, and is sometimes radioactive. Owing to those properties, it can be detected by means of very precise techniques (radioactive isotopes are traced by means of counters of electron or other nuclear particle emission).

The compounds into which isotopes of one element or another have been artificially introduced are absorbed and utilized in metabolic processes just like the same compound encountered in nature. By employing isotopes to label various compounds, the absorption of substances introduced into the stomach or intestine, and their further fate in the organism, can be observed.

The use of labelled compounds has enabled us to penetrate deeper into the problem of absorption and has made invaluable contributions to the study of metabolic processes.

#### ABSORPTION IN THE STOMACH AND SMALL INTESTINE

Absorption is a fairly slow process and can only be accomplished adequately with an extensive mucosal surface with which broken-down food can come in contact.

In the stomach absorption is limited, mineral salts, monosaccharides, alcohol, and water being absorbed here very slowly.

A comparatively small quantity of substances is absorbed in the duodenum where, as London's experiments showed, between 53 and 63 per cent of carbohydrates and proteins and a small amount of fat are digested. With gastric digestion taken into account, more than two-thirds of the total intake of protein and carbohydrate in food has been broken down in the duodenum; but only 5 to 8 per cent of the food is absorbed here, a quantity of little physiological importance, especially as concerns protein, since greater amounts enter the duodenum in the digestive juices than are absorbed within the same period.

Absorption occurs most actively in the small intestine where the absorptive surface is very large. Owing to the presence of an immense number of mucosal folds and processes, *villi*, its surface area is many times greater than the external body surface.

The membrane through which absorption takes place is formed from the *brush-border epithelium*, the cells of which have an elongated cylindrical shape and measure about eight microns in diameter by 25 microns in height. The cell surface facing the intestinal lumen has a narrow brush-like fringe one to three microns thick that can be seen under an ordinary microscope, and to which the cells owe their name. The electron microscope has revealed the structure of this fringe, which was found to be formed of the very fine, thread-like processes, *microvilli* (Fig. 89), one to three microns high and about 0.08 of a micron in diameter, within which pass microcanalliculi.

**FIG. 89. Microvilli of the brush-border epithelium in monkey's small intestine, viewed with the help of an electron microscope, X 66,000 (after N. M. Shestopalova)**  
1 — microvilli; 2 — microcanalliculi



The surface of a single cell has between 1,500 and 3,000 microvilli. They considerably increase the absorptive surface of the intestinal mucosa, bringing it up to an area of 500 square metres. It is here that the process of membrane digestion occurs (p.258).

Experiments in resecting the whole length of the small intestine below the duodenum show that the animals die quickly because no matter enters their blood from the intestine.

If the mucosa of an intestinal loop in an experimental animal is injured or poisoned (sodium fluoride is used for the purpose), and its viability in that way impaired to a certain extent, sharp disorders of absorption occur in the loop. Experiments of that kind demonstrate that absorption is associated with the normal physiological activity of the mucosal epithelium.

#### ABSORPTION IN THE LARGE INTESTINE

No significant absorption of nutrients occurs in the large intestine under normal physiological conditions, since most have been absorbed in the small intestine. The process, however, can take place here if a considerable amount of matter that can be broken down and absorbed enters the large intestine. The use of the so-called nutrient enema, i. e. the introduction of easily assimilated nutrients into the rectum, is based on this fact. The life of a person, however, cannot be maintained for any length of time in that way.

Water is absorbed intensively in the large intestine, so that disturbances in its condition lead to the passing of loose stools and loss of water from the organism.

#### MECHANISM OF ABSORPTION

Absorption is a complex physiological process by which various substances penetrate the epithelial membrane of the intestinal wall and enter the blood or lymph. They do not normally pass in the opposite direction, from the blood into the intestine, because of the one-way permeability of the epithelium. Filtration, diffusion, and osmosis play a definite role in the process.

The role of filtration is demonstrated by the dependence of absorption on the magnitude of the hydrostatic pressure produced in the intestine by mechanical contraction of the smooth muscles of its wall.

Direct experiments have shown that an increase of pressure inside the intestine of eight to ten millimetres of mercury doubles the rate of absorption of a solution of sodium chloride but at a pressure between 80 and 100 millimetres, absorption ceases owing to compression of the villi and of the blood vessels of the intestinal wall.

Diffusion and osmosis are of great importance for the process; the absorption of water from hypotonic solutions, for example, can be explained by the laws of osmosis. There are numerous facts, however, that contradict the assumption that absorption can be accounted for by simple processes of filtration, diffusion, and osmosis. If a dextrose solution of a lower concentration than that encountered in the blood is introduced into the intestine of a dog, water will be absorbed first until the concentration of the sugar solutions in the intestine and the blood is brought into equilibrium; then sugar begins to be absorbed. But if a glucose solution of higher concentration than the blood glucose content is introduced, the sugar is absorbed first, and only after that the water.

On the introduction of an isotonic sodium chloride solution into the intestine, salt is absorbed more rapidly than water and its contents become hypotonic. Blood serum, of an osmotic pressure the same as that of blood plasma, can also be absorbed.

Ingraham and Visscher studied the absorption of water and salts in experiments using isotope indicators and showed that the rate of water absorption from the intestine is a hundred times what would be encountered if diffusion and osmosis only were responsible for absorption. When the intestinal mucosa is injured, as by sodium fluoride, for example, absorption is governed completely by the laws of diffusion and osmosis and is sharply impaired. The concentration and osmotic pressure of solutions introduced into the intestine are then brought into equilibrium through the passage of water, salts ( $\text{NaCl}$  in particular), and other substances from the blood into

the intestine, though that is seldom encountered in normal physiological conditions.

The facts discussed above indicate that the epithelium is not simply a semi-permeable membrane, but is an organ with its own definite physiological function. Absorption is associated with the metabolism of the epithelial cells of the intestinal mucosa, as is evidenced by its dependence on temperature (it decreases with a fall in temperature) and oxygen supply. Poisons that inhibit various stages of energy metabolism suppress absorption.

Among the factors involved in the process contraction of the smooth-muscle fibres of the villi deserves mention. It exerts pressure on the lacteal vessels and produces a flow of lymph. Regurgitation of lymph into the lymphatic vessels of the villi does not occur because of the presence of valves in them. The movement of the villi, resulting in evacuation of the lacteals, at the same time causes the central lacteal to exert a sucking force on the intestinal contents and thus facilitates absorption.

Studies of the movement of the villi in various animals by means of micro-cinefilm have revealed that they are manifest in animals that have eaten, and do not occur in fasting animals; they may, however, be excited artificially, e. g. by puncturing the mucosa. The application of various substances to the mucosa can also cause contraction of the villi. The most important of these stimuli are substances that are continuously formed in the intestine as a result of normal digestion, such as protein breakdown products — peptides, alanine, leucine, and extractive substances, bile acids, and glucose. A special hormone that stimulates their movement, *villikinin* is formed in the duodenal mucosa. The fact that injection of blood, taken from a dog that has been fed, into the blood stream of a hungry dog causes movement of the villi in the second dog, points to the existence of humoral stimulation.

It is thought that contraction of the muscles of the villi is controlled by the Meissner nerve plexus located in the submucosal coat.

Peristaltic movements of the intestine also contribute to absorption by raising its pressure.

#### ABSORPTION OF PROTEINS

Amino acids, the final breakdown products of protein in the alimentary tract, are absorbed in the small intestine. A certain amount of protein may possibly also be assimilated through absorption of various polypeptides.

The chemical nature of protein breakdown products that are absorbed has been established by study of the amino acids in portal blood. This is done, for instance, by the *angiostomy technique* evolved by London, who proposed connecting a special cannula to the blood vessels, by means of which samples of blood could be col-

lected at any phase of digestion and the changes in its chemical composition studied.

*Angiostomy* is performed as follows: a thin metal tube is sutured to the external surface of the blood vessel; the other end of the tube is brought to the outside through the skin wound. After the animal has recovered from the operation, the blood required for examination can be collected by means of a syringe inserted into the tube.

Many experiments employing angiostomy have shown that the amino acid content of portal blood increases during digestion. Abel's method of *vividiffusion* has also supplied convincing evidence that amino acids enter the blood in the portal vein.

The method of *vividiffusion* consists in the following. Glass cannulas connected with thin collodion tubes submerged in a warm saline solution are inserted into the central and peripheral segments of a divided portal vein. Blood from the peripheral end of the vessel flows along the closed system of tubes and returns to the central venous segment.

Certain substances present in blood, for example, amino acids, glucose, etc., diffuse through the collodion tubes into the surrounding saline solution. Several grammes of amino acids can be derived from the solution by this method at the peak of digestion following a meal rich in proteins.

London demonstrated that a large amount of protein may be absorbed under normal physiological conditions in the form of comparatively simple polypeptides.

From 95 to 99 per cent of protein is digested and absorbed when the diet consists of proteins of animal origin, but only some 75 to 80 per cent when the proteins are of plant origin.

#### ABSORPTION OF CARBOHYDRATES

Carbohydrates are absorbed from the small intestine chiefly in the form of glucose and partly in the form of fructose and galactose. Absorption occurs slowly, and because of that the glucose content of portal blood does not exceed 0.3 per cent (the blood in other vessels contains 0.1 per cent). Glucose and galactose are absorbed most rapidly. They undergo phosphorylation (i.e. are combined with phosphoric acid) in the mucosa of the small intestine, which facilitates their absorption. In an animal poisoned by monoiodoacetic acid, which prevents phosphorylation, carbohydrate absorption is sharply retarded.

According to Faitelberg, the absorption of carbohydrates in the small intestine is stimulated by the pancreatic hormone insulin which influences carbohydrate metabolism in the body and causes a decrease in blood glucose content (p.381).

## ABSORPTION OF FATS

Experiments with animals given fats containing glycerol and fatty acids labelled with radioactive carbon ( $C^{14}$ ) have shown that their breakdown in the alimentary tract is insignificant (only 30 to 45 per cent of the fats that enter the intestine are hydrolysed), *triglycerides* of fatty acids being mainly broken down into mono- and di-glycerides and free fatty acids.

Unhydrolysed neutral fats, i.e. *triglycerides*, and *di-* and *mono-glycerides* and *salts of fatty acids* are partially absorbed.

Triglycerides are absorbed after emulsification by which a finely dispersed emulsion of minute drops of fat is formed.

Emulsification occurs through the effect of a complex compound consisting of salts of bile acids and products of fat-splitting (mono-glycerides and salts of fatty acids). The emulsified neutral fat is absorbed by the villi and enters the lacteals. Fatty acids and mono- and diglycerides formed on the breakdown of fat by lipase are partly resynthesized into neutral fats while passing through the epithelial layer and partly used for phospholipid synthesis.

Neutral fat is absorbed mainly by the lymph. Three to four hours after a meal rich in fat the lymphatic vessels are accordingly found to be abundantly filled with a milk-like lymph known as *chyle*. Only a small amount of the fat absorbed in the intestine enters the blood under normal conditions, predominantly glycerides of fatty acids with a short carbohydrate chain. Absorption, however, is maintained in a dog or cat with a ligated thoracic lymph duct, particularly after a meal rich in fats. The fat content of the blood flowing from the intestine along the portal vein is then higher than in the blood of the jugular vein.

## ABSORPTION OF WATER AND SALTS

Water enters the intestine with food and digestive juices. A total of five or six litres is received, as follows: one litre of saliva, 1.5 to 2.0 litres of gastric juice, 0.75 to 1.0 litre of bile, about 0.6 of a litre of pancreatic secretions, and one litre of enteric juice (i.e. a total of five to six litres). To that is added the daily intake of water (about two litres). Only about 150 millilitres of water, however, is discharged in the faeces, all the rest being absorbed into the bloodstream from the intestine. Absorption begins in the stomach, but proceeds most actively in the small intestine and colon.

A number of authors have studied the absorption of heavy water ( $D_2O$ ) that they introduced into the stomach and small intestine (because, being labelled, it could be followed), and established in that way that approximately ten times as much water is absorbed in the small intestine as in the stomach. Within ten minutes of the introduction of 50 millilitres of heavy water into the small intestine, 95 per cent of it had been absorbed.

Sodium, potassium, and calcium salts dissolved in water are mainly absorbed in the small intestine. Their absorption is governed by their content in the body ; for instance, with a fall in the amount of calcium in the blood it is absorbed at a much higher rate than normal.

#### THE FUNCTION OF THE LIVER IN ABSORPTION

The breakdown products of proteins and carbohydrates absorbed in the intestine pass to the liver with the portal blood, and there undergo complex chemical changes. The extreme importance of that aspect of hepatic activity has been shown in experiments on animals prepared by Eck's operation.

*Eck's operation* consists in ligating the portal vein and connecting it to the inferior vena cava, so that blood from the intestine by-passes the liver and directly enters the systemic circulation. If an animal so prepared is kept on a meat diet, it will die from poisoning by the toxic products of protein breakdown taken up from the intestine, which in normal conditions are detoxified in the liver.

The detoxifying *barrier function of the liver* consists in various types of synthesis that convert the toxic products carried in the portal blood into less noxious compounds. Thus, indole, skatole, and phenol, toxic substances formed by the activity of bacteria and absorbed by the blood in the colon are oxidized in the liver and combine with sulphuric and glucuronic acids to form the so-called paired *ether-sulphur acids*.

These processes in the liver concerned with the detoxification of intermediate metabolites are known as *defence synthesis*. Its importance as a barrier function is demonstrated by the following experiment: injection of an extract of the intestinal contents into the peripheral blood vessels of a dog gives rise to severe intoxication; the same extract causes no intoxication when injected into the portal vein.

#### SENSATIONS OF HUNGER AND THIRST

Hunger and thirst are unpleasant sensations, often even agonizing, that result from more or less prolonged deprivation of food and water. Their biological importance is that they are powerful factors impelling the organism to search for and take up food and drink.

#### THE SENSATION OF HUNGER

The sensation of hunger is an unpleasant feeling in the region of the stomach, usually described as "a hollow in the pit of the stomach", "gnawing pains in the stomach", and often attended with nausea and not infrequently with lassitude and weakness. The

feeling occurs periodically every 60 to 90 minutes, and lasts for 15 to 20 minutes. It usually appears when the stomach is empty, with the exception of the pathological hunger encountered with disorders in the condition of certain parts of the brain, and accompanied with the morbid voracity known as *bulimia*.

The sensation of hunger is associated with the extensive area of the central nervous system that Pavlov called "*the feeding centre*". The centre is a functional rather than an anatomical structure, and includes cells located in different regions of the cerebral cortex, in the subcortical nuclei, and in the reticular formation of the diencephalon, particularly in the hypothalamus. Its condition governs the sensations of hunger and satiety and its function is to control feeding behaviour, i.e. the finding and eating of food, and to exercise complex reflex control and co-ordination of the activity of the alimentary tract as a whole. The role of the hypothalamic nuclei and reticular formation was revealed in experiments on rats: stimulation of some of the nuclei located in the hypothalamus excited a heightened craving for food, while stimulation of others brought refusal to eat. The feeding centre is stimulated and inhibited both by stimuli arriving from various peripheral receptors, in particular from those located in the alimentary tract itself, and by humoral agents, i.e. by various chemical compounds reaching it in the blood.

Metabolic processes taking place in the nerve cells are evidently of importance to its activity. They stimulate or inhibit the feeding centre in much the same way that the carbon dioxide formed in the nerve cells of the respiratory centre stimulates it.

Two theories have been advanced to explain the physiological mechanism of hunger. One treats hunger as a general sensation whose occurrence is not so much associated with stimulation of the nerve endings in any organ, as caused by changes in the composition of the blood and in the state of various body organs, including the central nervous system. The fact that the feeling ceases if a nutrient easily assimilated by the cells, like glucose, is introduced into the blood, is a powerful argument in favour of the theory. But the same facts can easily be interpreted from the point of view of the other theory explaining hunger as a local sensation controlled by impulses reaching the brain from the interoceptors of the alimentary tract. According to this theory, the periodical activity of the alimentary tract is the basic mechanism responsible for the sensation of hunger.

#### PERIODICAL ACTIVITY OF THE DIGESTIVE ORGANS AND ITS RELATION TO HUNGER

Several of the digestive organs, particularly the stomach and intestine, are active not only after eating but also between spells of digestion. Periodical motor and secretory activity occurs in many

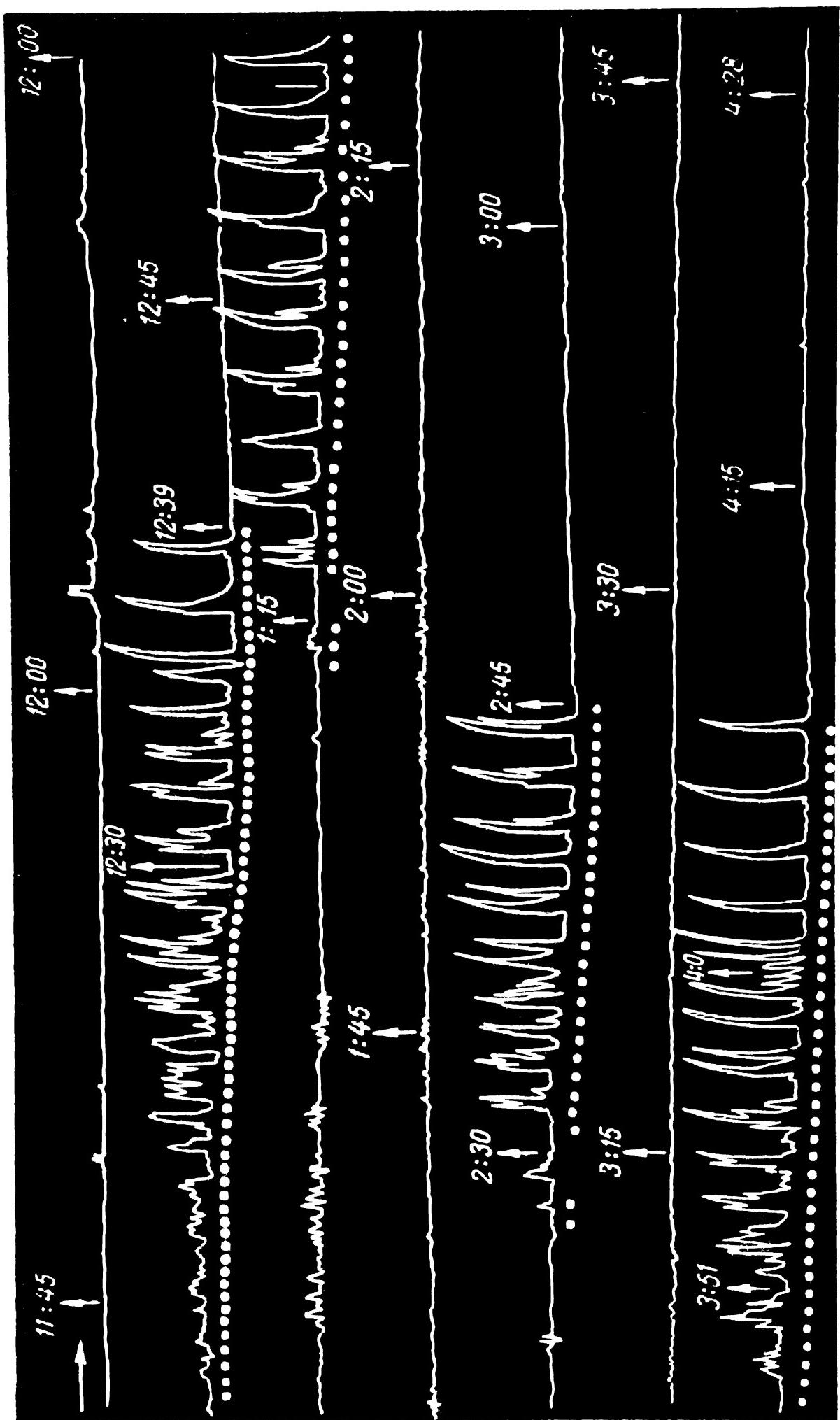
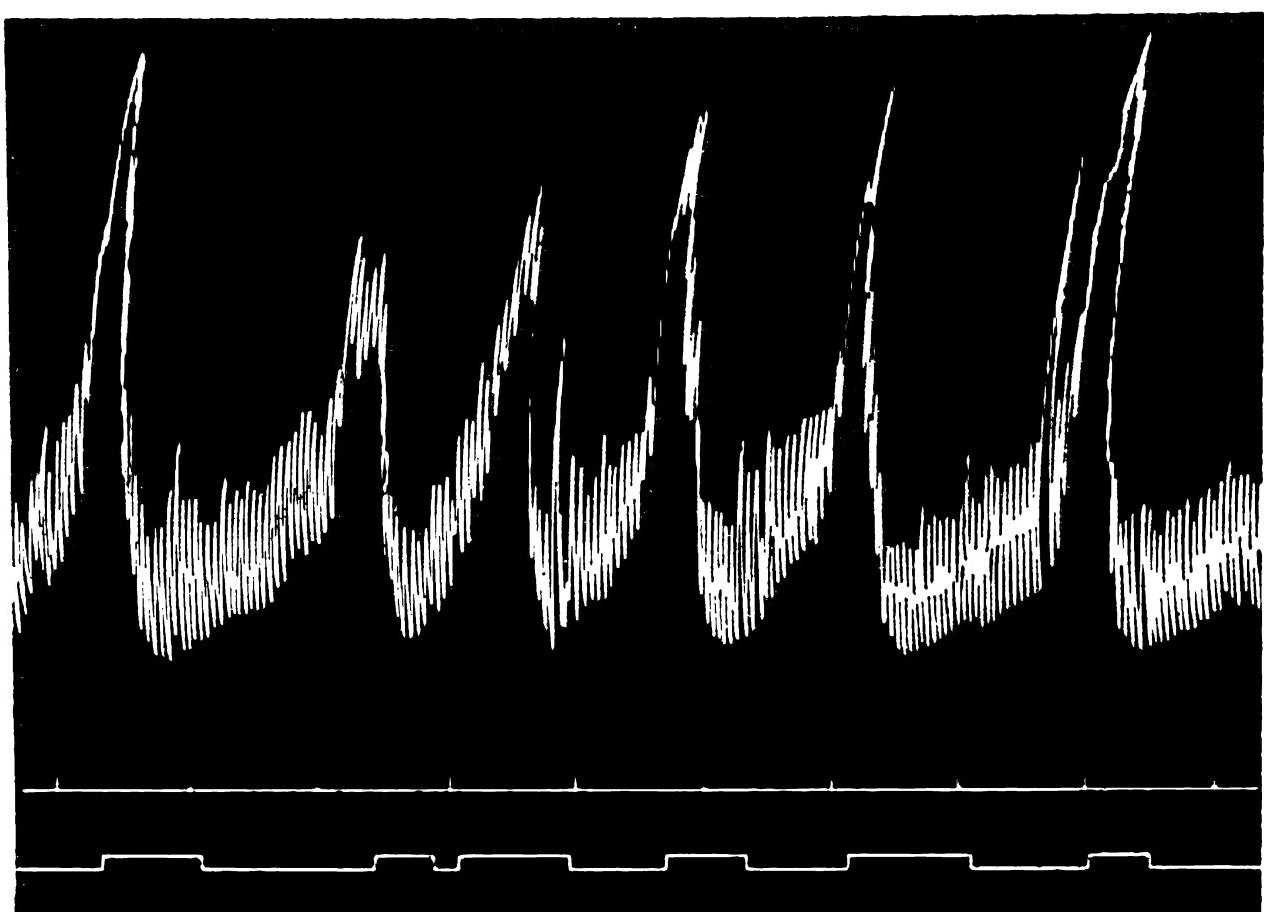


FIG. 90. Recording of periodical motor activity of the stomach occurring with no digestion taking place (after V. N. Boldyrev). The tracings show four periods of activity alternating with long periods of rest. Each line is a continuation of the other. The tracings are read from left to right and from top to bottom. The white dots under the tracings indicate the periods of duodenal secretion. The figures mark off the time



**FIG. 91. Relation between the hunger movements of the stomach and the sensation of hunger (after Cannon and Washburn)**

The top tracings show the hunger movements of the stomach; the middle line shows the time intervals (10 minutes) the bottom line shows the periods when the sensation of hunger occurs in the subject examined

organs when the stomach is empty. Boldyrev first revealed that a periodical cycle of contraction occurs in the empty stomach of a dog approximately every 90 minutes. The cycle lasts for 15 to 20 minutes and is followed by a period of rest (Fig.90). This periodical gastric motor activity is usually encountered with an alkaline stomach content and is accompanied with activation of movement in the duodenum and the small intestine, by duodenal and enteric secretions, and by a flow of bile from the bile ducts and gall-bladder.

The motor and secretory activity occurs simultaneously and are accompanied with certain changes in body activity, e.g. changes in respiration and circulation, an increase in the excitability of the nervous system, etc.

Cannon, Carlson, Anichkov, and others showed that a similar periodical activity is encountered also in man. Study of this gastric motor activity led several researchers to conclude that it was the periodical contraction of the stomach and intestine that induced the sensation of hunger; for that reason they were called "hunger contractions". They are synchronous with the feeling of hunger (Fig.91).

That a connection exists between these two phenomena is suggested by the fact that factors inhibiting periodical movements reduce the feeling of hunger. Strenuous muscular exercise and prolonged abstinence from food over a period of many days have that effect which explains why subjects who are severely exhausted or have fasted for days do not feel hungry (those who had fasted for a number of days note that they suffer agonizing hunger only during the first three or four days).

Chukichev found that periodical gastric contractions are stimulated in an animal by the introduction of blood taken from a fasting one; injection of blood from an animal that had been previously fed inhibited or even completely arrested the hunger contractions. Those facts indicate that the stimulus responsible for excitation of periodical activity is the "hunger" composition of the blood, in other words, the appearance in it of humoral stimuli due to the changes in metabolism encountered in the absence of digestion.

The injection of glucose into the blood causes the disappearance of periodical activity of the alimentary tract and of the sensation of hunger.

The hypothalamic nuclei have an important role in causing periodical activity of the digestive organs. Bogach showed that their stimulation excites motor activity of the alimentary tract.

In accordance with current physiological conceptions, it may be supposed that changes taking place in the composition and properties of the internal medium of the body act as humoral stimuli of the hypothalamic nuclei which are sensitive to the shifts in body chemical activity, that gives rise to the periodical activity of the digestive organs. That activity in turn evokes a flow of impulses from the receptors of the stomach and intestine to the higher parts of the central nervous system and causes the feeling of hunger.

## THIRST

Thirst arises through an inadequate supply of water to the body, excessive intake of salts (for example, salty foods) or great loss of water (as a result of profuse sweating, the effect of diuretics, etc.). The physiological reaction to the feeling of thirst is to drink water, and in this way the sensation contributes to maintenance of a constant water balance and equilibrium of electrolyte in the organism.

According to one theory, thirst is a general sensation. The way it arises can be attributed to the stimulation of special receptors sensitive to a rise in osmotic pressure, through reduction of the water content of the organism. The receptors, known as *osmoreceptor cells*, have been found, in particular, in the hypothalamus.

From that point of view, the sensation of dryness in the mouth and throat that accompanies thirst is a secondary phenomenon.

Rinsing of the mouth and throat with water only alleviates the sensation a little but does not bring complete relief. The sensation can be completely suppressed if a hypotonic solution is injected into the blood, or if water is introduced into the rectum. That has been observed in people who have lost much water, for example, after profuse sweating or copious elimination of water from the intestine (in cholera). Observations of an oesophagotomized dog also favour the assumption that thirst is a general sensation. The dog can drink for a long time but as water flows from the divided oesophagus and does not reach the organism thirst is obviously not quenched that way; but the introduction of a quite small amount of water into the stomach relieves it (Zhuravlev).

To that theory is counterposed another that considers thirst a local sensation associated with dryness of the mouth and throat mucosa and with the stimulation only of the receptors lodged there. The following facts are advanced in support of this view. The feeling of thirst is quickly abolished by painting the pharynx with cocaine, which reduces the excitability of the sensory nerve endings. Dogs that have been deprived of water for several days refused to drink after the pharynx was treated with cocaine. The introduction of atropine, another toxic substance which arrests the secretion of saliva and causes dryness of the mouth and throat as a consequence, is attended with a feeling of thirst, although the organism may not actually be suffering loss of water.

Cannon holds that the sensation of thirst is associated with a decrease in secretion of saliva, leading to dryness of the mouth and throat. The amount of saliva secreted is to some extent governed by the amount of water in the organism. Loss of water from the tissues is followed by a decline in saliva secretion. The feeling of thirst appears when the secretion decreases by 20 per cent, and becomes intolerable if it falls to 50 per cent. That view is particularly supported by the fact that thirst is appeased by pilocarpine, a poison that causes copious salivation. In Cannon's opinion, the relief of thirst by an intravenous injection of water is due to restoration of normal saliva secretion and abolition of the sensation of dryness in the mouth and throat.

The feeling of thirst occurring in response to reduction of the water content of tissues and prompting drinking and the restoration of homeostasis most probably has a complex mechanism. It is perceived subjectively as a feeling of dryness of the mouth and throat mucosa; consequently, impulses arising in the receptors there play a role in its occurrence. On the other hand, the osmoreceptor nerve cells of the hypothalamus where the centre of water balance is located play an important part in its development. Excitation of that centre by stimulation of the osmoreceptors leads to a decline in the amount

of water eliminated from the organism and to reduction of salivary secretion, which causes the sensation of dryness in the mouth and throat.

According to Zhuravlev, there is a “*drinking centre*” similar to the feeding centre in the brain. The sensation of thirst is controlled by that centre, which is formed by an aggregate of neurones lying in the cortex of the cerebral hemispheres, in the subcortex, and in the nuclei of the hypothalamus where the centre controlling water balance is located.

## Chapter 7

### NUTRITION. METABOLISM AND ENERGY EXCHANGE

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We have already considered the importance of metabolism as an essential function of living organisms and a distinguishing feature of life (p.38). Through the metabolic processes constantly taking place in all cells there is a continuous formation, disintegration, and renewal of cell structures and intercellular matter, so that there is a constant breakdown and synthesis of different chemical compounds in the organism, with substances of one kind being transformed into others. There also occurs a transfer of energy, a transformation of the potential energy of chemical compounds, which is released through their breakdown, into kinetic forms, primarily thermal and mechanical, but partially also electrical.

To make good the expenditure of the organism, preserve body mass, and meet the requirements of growth, proteins, fats, carbohydrates, vitamins, mineral salts, and water must be obtained from the environment in quantities and quality that correspond to the state of the organism and its conditions of existence. That is achieved through *nutrition*. There is a further requirement, to purge the organism of the end products formed during the breakdown of these different substances, which is accomplished by the organs of *excretion*.

In physiology we are not concerned with the whole course of the processes of metabolism, i.e. with the dynamics of the chemical changes taking place in the cells, which is the concern of biological chemistry. Physiologists usually limit themselves to determining the material and energy expenditure of the organism, and establishing what

substances it requires and how its requirements are to be met qualitatively and quantitatively through adequate nutrition.

In our further treatment of the subject we shall consider the metabolism of proteins, fats, carbohydrates, and mineral salts separately, and shall also discuss the significance of the various vitamins. The transformation of all these materials occurs simultaneously in the organism, of course, and their separation is an artificial division of the individual parts of a single biological process. It is necessary, however, for convenient treatment, and also because the substances enumerated have different physiological functions. In pathological conditions, moreover, changes and disturbances can occur that predominantly involve protein or fat metabolism, carbohydrate metabolism, or mineral-water metabolism.

#### PROTEIN METABOLISM

Protein has a dual importance for the organism, as a building material and as a source of energy. Its *plastic significance* is that it is utilized to form various cell structures in parts of which it is a necessary component. Its *energy significance* is that it provides the organism with energy liberated through its breakdown and utilized in life processes.

The breakdown of protein, and the formation of chemical compounds not utilized any further by the organism and excreted by it, occur regularly and without interruption. Since proteins are synthesized in the animal organism only from amino acids and polypeptides, which it does not form from other substances, the organism has to obtain them in its food. Only in that way can it make good its consumption of protein and ensure the replacement of disintegrated cells (like the formed elements of the blood, the epithelial cells of the skin and of the mucous membrane of the intestine, etc.) by newly formed ones. Protein requirements are particularly heavy, of course, in periods of growth when the mass of the cells in the organism is being increased.

Protein is synthesized in the cells from amino acids and low-molecular polypeptides which are formed in the alimentary tract through the breakdown of the proteins in food and absorbed into the blood.

Tissue proteins are never in a static state, but are constantly undergoing disintegration or synthesis, as has been shown by Schoenheimer and others through the introduction of tracers via the nitrogen of amino acids. By introducing leucine labelled with N<sup>15</sup> into rats, it was found that 70 per cent of the N<sup>15</sup> had been taken into tissue proteins within three days, while around 30 per cent had been excreted. The highest percentage of labelled nitrogen was found in the proteins of the blood plasma, the lining of the intestine, kidneys, pancreas, and liver.

## NITROGEN BALANCE

Because the distinctive feature of the composition of proteins, differentiating them from fats and carbohydrates, is the presence of nitrogen, the overall results of protein metabolism, i.e. the quantity of proteins taken into the organism and broken down in it, can be estimated from the value of the *nitrogen balance*. This term shows the difference between the quantity of nitrogen obtained by the organism from its food and that excreted in its urine and sweat. We can judge the intake and consumption of nitrogen from the value of the nitrogen balance first, because the nitrogen in food is overwhelmingly in proteins (only a small amount entering into the composition of other nutrients, such as nucleic acids, extractive substances, and vitamins) and, second, because the nitrogen excreted from the organism comes predominantly from the breakdown of proteins in the body.

Since not all the nitrogen in food is assimilated by the organism and part of it is excreted in the faeces, it is necessary to determine the actual amount taken up and *assimilated*, by subtracting the quantity in the faeces from the total contained in the food. Knowing how much nitrogen has been assimilated, we can calculate how much protein has been taken up by the organism, on the basis that the nitrogen content of protein varies between 14 and 19 per cent, averaging about 16 per cent (i.e. 6.25 grammes of protein contain one gramme of nitrogen). Multiplying the amount of nitrogen by 6.25 will therefore give us the quantity of protein. To determine how much protein is broken down, however, we must establish the nitrogen content of the urine and sweat, since nitrogenous breakdown products are secreted both by the kidneys and by the sweat glands. The insignificant amount of nitrogen in sweat, however, permits us to ignore it in most cases, so that estimation of the expenditure of proteins can usually be limited to determination of the quantity of nitrogen excreted in the urine.

If more nitrogen is taken up than is excreted, the organism has a *positive nitrogen balance*, that is, there is a preponderance of protein synthesis over breakdown. An excess of excretion over uptake by the organism, on the contrary, is evidence of a *negative nitrogen balance*, and of a preponderance of protein breakdown.

A negative nitrogen balance is encountered in starvation and in conditions when the organism does not obtain certain amino acids that are indispensable for protein synthesis.

## PHYSIOLOGICAL IMPORTANCE OF THE AMINO ACID COMPOSITION OF FOOD PROTEINS

Normal protein metabolism and synthesis require various amino acids in the diet. The importance of individual amino acids for the organism, and their influence on the state of the nitrogen balance,

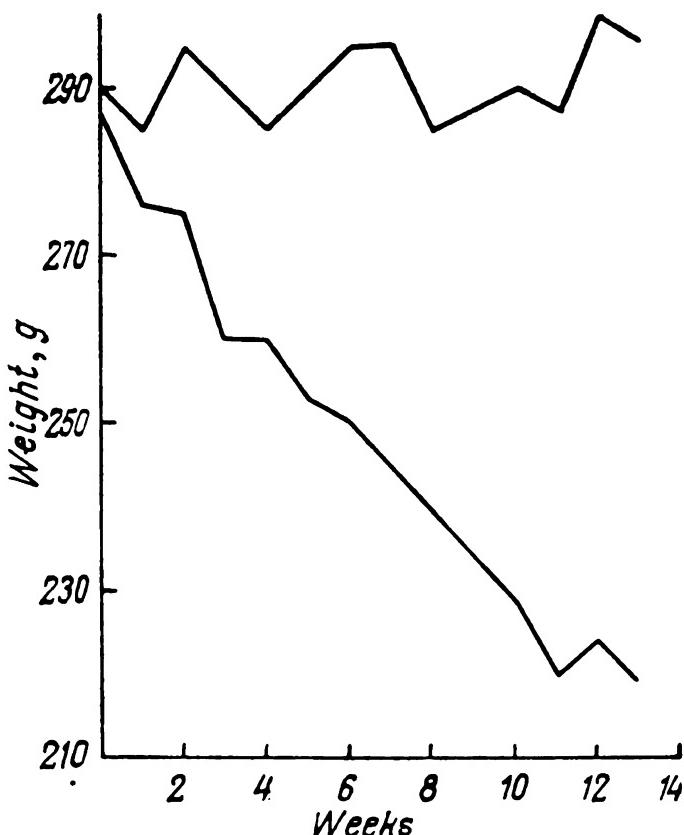


FIG. 92. Curves of changes in the body weight of rats kept on a diet of corn protein (zein) to which tryptophane (bottom curve) or tryptophane and lysine (top curve) were added (after Neuberger et al.)

growth, weight, and general condition of animals can be judged by varying their ratios in the diet or by excluding one amino acid or another. It has been established experimentally that ten of the twenty known amino acids can be replaced by others, while the remaining ten are indispensable.

The *indispensable amino acids* include those that are not formed in the animal organism, protein synthesis is sharply impaired in their absence and a negative nitrogen balance, arrest of growth, and loss of weight are encountered. Animals cannot live long and their condition cannot be normal if only one of the following acids is missing from the diet: leucine, isoleucine, valine, methionine, lysine, threonine, phenylalanine, histidine, arginine, and tryptophane. Apart from impairment of protein synthesis and a negative nitrogen balance an organism deprived of certain of these amino acids may suffer peculiar disorders the character of which depends on the role played by the amino acid. Tryptophane, for instance, is essential for a normal pregnancy. If a rat is given food not containing tryptophane after fertilization, the embryo will undergo intra-uterine resorption by the fourteenth day. Disturbances of balance and disorders of the nervous system were encountered in mice fed on a diet from which valine was excluded. In the absence of lysine growth was arrested and loss of body weight occurred (Fig. 92).

The other amino acids are *dispensable*; tyrosine, for instance, can be replaced in the foodstuffs by phenylalanine from which it is formed in the body.

## BIOLOGICAL VALUE OF PROTEINS

Since proteins differ in their amino acid composition, the possibility of using them for synthesis in the organism also varies. Because of that, the concept of their *biological value* has been introduced. Proteins containing the entire complex of necessary amino acids in proportions that will ensure normal processes of synthesis are considered biologically valuable. Those that lack some amino acid or another, or those that contain them in slight amounts, are considered inadequate; thus gelatin which contains only traces of cystine and no tryptophane or tyrosine, zein (a protein present in maize) which is poor in tryptophane and lysine, gliadin (a wheat protein) and hordein (a barley protein) which contain small quantities of lysine, and a number of other proteins are inadequate. The proteins of meat, eggs, fish, roe, and milk are of the highest biological value.

The biological value of any protein varies from person to person. Apparently, it has no definite static value but alters according to the condition of the organism, the dietary regimen previously followed, the intensity and character of physiological activity, age, the individual and species features of metabolism, and other factors.

It is of practical importance, however, that two inadequate proteins, one of which lacks certain amino acids and the second lacks others, can together meet the requirements of the organism.

## BREAKDOWN OF PROTEINS IN THE ORGANISM

The breakdown of proteins and the elimination of nitrogen from the organism occur continuously both when proteins are ingested in food and during starvation. The amount of nitrogen eliminated and, consequently, the quantity of tissue protein that has been broken down, vary with the character of the food. Minimum protein expenditure is encountered with a carbohydrate diet and in protein starvation. With abundant introduction of starch and sugar into the body and when the diet contains no proteins the elimination of nitrogen may be only a third (30 to 33 per cent) of that encountered in complete starvation. The carbohydrates in this case exert a so-called *protein-sparing action*.

The breakdown of protein occurring in the organism when the diet is free of proteins but contains adequate quantities of all the other nutrients (carbohydrates, fats, mineral salts, water, vitamins) indicates the minimum protein requirement associated with the basal processes.

The minimum protein loss of an adult resting body, calculated per kilogram of body weight, averages between 0.028 and 0.065 gramme of nitrogen per kilogram of body weight per 24 hours. That means that an individual weighing 70 kilograms loses between two and 4.5 grammes of nitrogen every 24 hours,

which corresponds to the breakdown of 12.5 to 28 grammes of protein.

The most important nitrogenous breakdown products which are eliminated in the urine and sweat are urea, ammonia, and uric acid.

Part of the  $\text{NH}_3$  formed on deamination from the  $\text{NH}_2$  fraction of amino acids is excreted by the kidneys, but the larger part is converted into urea in the liver and then also excreted by the kidneys. That urea and ammonia are both formed in the liver is indicated by the fact that the  $\text{NH}_3$  content of portal blood is three times that of the blood in the hepatic veins, as had been established by Pavlov, Nencki, and Zalesky in 1895. The formation of urea ceases when the liver is removed.

$\text{NH}_3$  and  $(\text{NH}_4)_2\text{CO}_3$  are toxic to the organism, while urea is a fairly harmless metabolite; therefore urea synthesis in the liver is of great significance for the organism.  $\text{NH}_3$  is also detoxified by being utilized to form the amide group of glutamine.

Other nitrogenous substances like uric acid or 2, 6, 8-trioxypurine are also eliminated in the urine. Uric acid enters the blood directly from the tissues, being a product of nucleic acid breakdown. Slight quantities of other, less oxidized, purine substances are eliminated in the urine, namely, adenine (6-aminopurine) and guanine (2-amino-6-hydroxypurine) and their derivatives hypoxanthine (6-oxy-purine) and xanthine (2, 6-dioxypurine). Creatine and its anhydride creatinine are other nitrogenous breakdown products excreted in the urine.

#### NITROGEN EQUILIBRIUM

An intake of proteins in food increases the elimination of nitrogen from the organism because protein raises its energy expenditure, which shows their specific dynamic action (p.322).

When the amount of nitrogen in food is so low that it corresponds to the minimum protein loss, the nitrogen balance is negative. By increasing the amount of protein consumed a condition can be established in which nitrogen intake and output are equal, a physiological state known as *nitrogen equilibrium*.

If protein intake is increased after nitrogen equilibrium has been established, equilibrium will be quickly re-established, but at a higher level of protein utilization and breakdown. That is because proteins are not stored in the body; when food is rich in them some are utilized to replace destroyed tissue proteins, but most are deaminized and utilized as sources of energy; the nitrogenous products formed through the breakdown of tissue proteins and the deamination of assimilated proteins are excreted. As a result, the quantities of nitrogen assimilated and excreted become almost equal, and the balance is very low, even about zero. Hence it is clear that a

nitrogen equilibrium is established with various amounts of protein in the diet, both fairly low and very high. In experiments on dogs a nitrogen balance was observed with daily rations over a long period as low as 480 grammes of meat and as high as 2,500 grammes.

#### RETENTION OF NITROGEN

In certain physiological conditions, when the organism's requirements of protein are completely satisfied but they are still consumed in excess, the nitrogen balance becomes positive, i.e. *retention of nitrogen* occurs. Retention is encountered in growing organisms, owing to the increasing body mass, and during pregnancy owing to the growth of the foetus. It is also observed when processes of synthesis are intensified so as to replace cell proteins previously broken down, e.g. during convalescence after a severe illness.

Strenuous training in sports leading to an increase in the bulk of muscle tissue is also attended with nitrogen retention.

Low retention occurs with any sharp rise in nitrogen intake and is accompanied with an accumulation of protein which is, however, very rapidly utilized by the organism (this protein is known as the "expendable" or "reserve" protein).

#### PROTEIN STARVATION

A state of *protein starvation* is encountered with a protein-free diet, or when the proteins contained in it are either deficient in quantity or inadequate in quality.

Protein starvation is marked by a gradual, progressive loss in body weight, even though the intake of fats, carbohydrates, salts, water, and vitamins is adequate, because expenditures of tissue proteins (minimum under these conditions and equal to the depreciation coefficient) are not compensated by those in the diet. Consequently protracted protein starvation, like total starvation, inevitably ends in death. The condition is particularly serious in growing organisms, in which there is not only loss in body weight but arrest of growth owing to the deficiency of plastic material essential for building cell structures.

#### CONTROL OF PROTEIN METABOLISM

There are data that point to the existence of special centres concerned with control of protein metabolism in the hypothalamic region of the diencephalon. Experimental injury to definite hypothalamic nuclei results in a sharp increase in the amount of nitrogen eliminated in the urine, which indicates a significant activation of protein breakdown; even an enriched diet does not protect the animal from emaciation.

The way the nervous system acts on the protein metabolism of tissues would seem, in all probability, to be as follows. The nervous system influences the secretion of hormones by the endocrine glands and their discharge into the blood, in particular, secretion of the thyroid hormones thyroxine and tri-iodothyronine (p.373), which in turn evokes changes in protein metabolism in the tissues. The somatotropic hormone of the anterior lobe of the pituitary gland also has a marked effect in this respect.

### LIPID METABOLISM

The physiological role of lipids — fats, phosphatides, and sterols — is that they are components of the cell structures essential for the building of new cells (*plastic significance of lipids*), and also that they are utilized as rich sources of energy (*energy-yielding significance of lipids*).

### FAT METABOLISM

The fats of animal organisms are triglycerides of oleic, palmitic, and stearic acids, and of certain other higher acids.

Most fat occurs as adipose tissue; a smaller part is a component of cell structures. The fat forming part of the structure of the cell-membrane, protoplasm, and nucleus often cannot be seen by direct observation of histological specimens. In contrast, the fat occurring in cells as inclusions is easily revealed microscopically and microchemically. The droplets encountered in the cells are reserves of fat that are utilized when energy is required. Particularly large reserves of fat are held in the adipose tissue which is found mainly in the subcutaneous cellular tissue, around certain internal organs (e.g. in the perinephric tissue around the kidneys) and in certain organs like the liver and muscles.

*The total amount of fat* in the human organism varies widely, but constitutes between 10 and 20 per cent of the body weight on average; it may, however, be as much as 50 per cent in cases of pathological obesity.

The amount of depot fat depends upon the character of the diet, the quantity of food, constitutional features, sex, age, etc., but the amount of protoplasmic fat is constant and invariable.

**The formation and breakdown of fats in the body.** Most of the fat absorbed from the intestine enters the lymph, and only a small amount enters the blood directly.

Experiments with animals given labelled fats containing carbon and hydrogen isotopes have demonstrated that the fat absorbed in the intestine directly enters the adipose tissues which serve as fat depots for the organism. The fats encountered there may pass into

the blood and reach the tissues, where they undergo oxidation, i.e. are utilized as sources of energy. The liver plays a major part in fat metabolism.

The fats of various animals, like the fats of the different organs, differ in chemical composition and physico-chemical properties (melting-point, consistency, saponifiability, iodine value, etc.).

Animals of any one species have fat of relatively constant composition and properties which is a manifestation of their species specificity.

With a diet containing small amounts of fat, fat characteristic of the species concerned is laid down in the body of an animal or man. Species specificity, however, is much less marked with fats than with proteins.

Prolonged and abundant feeding with one kind of fat can cause changes in the composition of the fat laid down in the body. The relationship between the composition of the fat in food and that of subcutaneous fat has been shown by Lebedev's experiments on two dogs that had lost almost all their reserves of body fat by being starved for a long time. One of the animals was then fed linseed oil, the other mutton fat. Both animals regained their weight in three weeks, and were then killed. About one kilogram of fat was found deposited in the body of each animal; in the first dog this fat had a fluid consistency, did not set at 0°C, and resembled linseed oil; in the second dog the fat was hard, with a melting-point of 50°C, and resembled mutton fat.

The influence of the fat in food on the properties of human fat has also been noted. For instance, with a diet including mutton fat, the melting-point of subcutaneous fat rises, approaching its melting-point. It has been found that the subcutaneous fat of Polynesians, who eat much coco-nut oil, is close to that oil in its properties, while the subcutaneous fat of individuals who eat seal meat is close in properties to seal oil.

In the opinion of some researchers, the fat that is specific to a given organism is formed in the intestinal epithelium; others hold that it is formed in the cells of the liver and other organs.

With a fat-free diet rich in carbohydrate fat is synthesized from the carbohydrates. The fattening of animals practiced in agriculture provides evidence of that.

Certain unsaturated fatty acids (those with more than one double bond), like linoleic, linolenic, and arachidonic acids, are not formed in the bodies of man and certain animals but are nevertheless essential for normal vital activity. Because of that, and also because certain vitamins are supplied to the body dissolved in fat (p.299), grave pathological conditions can be encountered following prolonged deprivation (over a period of many months) of fats. These conditions are treated by a diet rich in fats.

## CONTROL OF FAT METABOLISM

That fat metabolism is regulated by the nervous system is demonstrated by the fact that various disorders occur in this process when the hypothalamic nuclei are damaged. Thus, obesity is encountered in animals suffering injury to the ventromedial nucleus and extreme emaciation in those with injured lateral nuclei. Postmortem examination has revealed a lesion of the tuber cinereum of the hypothalamus in subjects with certain kinds of severe pathological obesity. The influence of the nervous system may be effected through changes in the internal secretion of the pituitary and thyroid glands, the pancreas, and sex glands. It is also possible that it has a direct effect on fat metabolism in the tissues.

The grounds for that assumption are the results of experiments on mice and rabbits with unilateral dissection of the nerve supplying the fat accumulated in the space between the shoulder-blades. Utilization of the fat on the denervated side was impaired; during starvation fat was retained in the denervated adipose tissue although the animal became extremely emaciated and all its fat depots had already been used up. The action of the nervous system on fat metabolism may be considered an example of the trophic function of the nervous system (see Vol. II, Chapter 13, Trophic Function of the Nervous System).

The hormonal control of fat metabolism has been observed in experiments on injecting hormones from the pituitary gland, thyroid, pancreas, and sex glands into animals and by removing those glands. Clinical observations have also yielded much data on the influence of the endocrine glands, it having been established, for instance, that deficiencies of the pituitary gland, thyroid, and sex glands are attended with obesity. Injection of insulin, the pancreatic hormone (p.381), increases the formation of fat from carbohydrates.

## METABOLISM OF PHOSPHATIDES AND STEROLS

Foods rich in fats usually contain certain quantities of phosphatides and sterols, which are of very great physiological importance being constituents of cell structures, particularly of the membranes of many cells, and of nuclear substances and protoplasm.

The nervous system is especially rich in phosphatides which apparently play an important role in its activity.

Phosphatides are synthesized in the intestinal wall and in the liver (an increased phosphatide content is found in the blood of the hepatic vein). The liver is a depot for lecithin which is found there in quantity after a meal rich in lipids.

Phosphatides are synthesized from neutral fats, phosphoric acid, and the nitrogenous base choline. Lecithin cannot be formed in the liver if food does not contain choline or methionine, an amino acid

that gives up the methyl groups needed to synthesize choline in the organism, and a disturbance of fat metabolism, fatty infiltration of the liver, occurs. The fat content of the liver may then be as high as 50 per cent instead of the normal 5 per cent.

Sterols, cholesterol in particular, are of exceptional physiological importance. Cholesterol is a source from which the hormones of the adrenal cortex (p.387) and of the sex glands (p.393) are formed. Certain sterols, like vitamin D, possess a high physiological activity.

### CARBOHYDRATE METABOLISM

The significance of carbohydrates for the organism as a source of energy is due to the rapidity with which they are broken down and oxidized, and the ease with which they are liberated from the depots. They can thus be drawn on when the organism requires additional and rapidly increasing amounts of energy, as during emotional excitement (anger, fear, pain), strenuous muscular effort, or convulsions, or under conditions that cause a sharp drop in body temperature. Carbohydrates are extremely important in the metabolism of the muscles.

The significance of carbohydrates as a source of energy can be seen in the fact that with the decrease in the blood sugar level known as *hypoglycaemia*, body temperature falls and there is muscular weakness attended with a feeling of fatigue. Severe hypoglycaemia can terminate in death.

Carbohydrates are also important for the metabolism of the central nervous system, as the occurrence of severe disorders in its normal functioning following a fall in the blood sugar level to 40 milligrams per cent (the normal value averages 100 milligrams per cent) indicates. Convulsions, delirium, loss of consciousness, and changes in the state of the organs innervated by the vegetative nervous system can occur, with pallor or redness of the skin, sweating, disturbances of cardiac activity, etc. All these unfavourable hypoglycaemic symptoms are relieved within a short time once a glucose solution has been introduced under the skin, into the blood, or per os, or ordinary sugar is given to the patient to eat.

### CARBOHYDRATE ALTERATIONS IN THE ORGANISM

Glucose passing into the blood from the intestine is carried to the liver, where *glycogen* is synthesized from it. If a liver removed from the body is perfused with a Locke solution containing glucose, its glycogen content will increase.

Glycogen is formed not only from glucose, but also from products of intermediate carbohydrate breakdown which are resynthesized into glucose; phosphorylation of glucose occurs during the process of glycogen synthesis.

The glycogen in the liver is a reserve carbohydrate. In an adult, its level may be as high as 150 to 200 grammes. With a relatively slow supply of sugar to the blood, it is formed quite quickly, so that the introduction of small quantities of carbohydrate does not lead to an increase in blood sugar content (*hyperglycaemia*); but it grows rapidly if a large amount of easily broken down, and therefore readily absorbable, carbohydrate is introduced into the alimentary tract or if a large quantity of glucose is injected into the blood. The hyperglycaemia that develops in such cases is known as *alimentary*, and results in *glycosuria*, i.e. elimination of sugar in the urine owing to decreased re-absorption of glucose in the kidneys.

Glycosuria is encountered when the level of sugar in the blood rises to between 150 and 180 milligrams per cent.

With a diet completely free of carbohydrates they may be formed in the body from proteins and fats. It has been shown that more than half of the total number of the products of deamination of aliphatic amino acids can be converted to glucose, but carbohydrates cannot be formed from amino acids of the cyclic series.

As sugar level of the blood declines, glycogen is broken down in the liver and glucose liberated into the blood stream (a process known as the *mobilization of glycogen*), so that the blood glucose content is maintained at a relatively constant level (80 to 120 milligrams per cent).

Glycogen is also stored in the muscles, where its content is 1 or 2 per cent, but increases with lavish feeding and decreases during fasting. Muscular work leads to intensification of glycogen disintegration. Under the influence of the enzyme phosphorylase, which is activated at the beginning of muscular contraction, molecules of phosphoric acid combine with glycogen and it breaks down to glucose-1-phosphate, which is one of the sources of energy responsible for the contraction of the muscles.

The withdrawal of glucose from the blood stream varies from organ to organ: according to London, the brain retains 12 per cent, the intestines 9 per cent, the muscles 7 per cent, and the kidneys 5 per cent.

Certain organs (the spleen and the lungs) do not retain glucose at all, but utilize glycogen which is brought to them in small quantities in the blood.

Carbohydrates are broken down in the animal organism both in the absence of oxygen (*anaerobic glycolysis*) and by the oxidation of the breakdown products of carbohydrate to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  (*aerobic glycolysis*).

Both anaerobic and aerobic breakdown of carbohydrates are attended by phosphorylation, which is an essential link in the processes concerned with breakdown of carbohydrates in the organism and utilization of the energy of those compounds.

### **CONTROL OF CARBOHYDRATE METABOLISM**

The influence of the nervous system on carbohydrate metabolism was first revealed by Claude Bernard, who discovered that a puncture of the medulla oblongata at the floor of the fourth ventricle (diabetic puncture) caused mobilization of the carbohydrates stored in the liver, with subsequent hyperglycaemia and glycosuria. The highest centres concerned with the control of carbohydrate metabolism lie in the hypothalamus, stimulation of which causes changes similar to those produced by Bernard's puncture.

The centres of carbohydrate metabolism influence the periphery mainly through the sympathetic nervous system. An important role in effecting that is played by adrenaline which, being formed on stimulation of the sympathetic nervous system, acts upon the liver and muscles and causes mobilization of glycogen.

Carbohydrate metabolism is influenced by the cerebral cortex, which is evident from the fact that the sugar level rises in the blood and slight quantities of sugar may even be eliminated in the urine in students after a difficult examination, spectators at a football match, and reserve players who, though not playing, are concerned for the success of their team.

The humoral control of carbohydrate metabolism is extremely complicated. The pancreatic hormones insulin and glucagon (pp. 381-382) are responsible for it along with adrenaline. A certain influence is also exerted by hormones secreted by the pituitary gland, adrenal cortex, and thyroid.

### **METABOLISM OF MINERAL SALTS AND EXCHANGE OF WATER**

#### **THE IMPORTANCE OF MINERAL SALTS AND WATER FOR THE ORGANISM**

Water and mineral salts enter into all the essential physico-chemical processes occurring in the organism. The concentration of the mineral salts dissolved in water, for example, is responsible for the value of osmotic pressure in the blood and tissue fluids, maintenance of which at a constant level is indispensable for normal vital activity. Inorganic substances also contribute to maintenance of acid-base equilibrium and of a relatively constant pH of the blood and tissues. Mineral salts and water are involved in the phenomena of diffusion and osmosis that play a role in the processes of absorption and excretion. In addition, they preserve the colloidal state of living protoplasm. Changes in the amount of water in the organism and shifts in the salt composition of body fluids and tissue structures impair the stability of the colloids and can lead to irreversible disturbances in, and even to the death of, individual cells or of the organism as a whole.

Deprivation of water and salts leads to grave disorders and death. A person deprived of water may die within a few days, which should

be compared with the fact that a starving man who has an unlimited supply of water can live for as long as 40 to 45 days. With complete starvation the loss in body weight may be as much as 40 per cent, but with deprivation of water a loss of even 10 per cent brings on severe disturbances, while a loss of 20 to 22 per cent of the body weight is fatal.

The importance of mineral salts was established by direct observations. Animals kept on a diet containing all the necessary nutrients and water but devoid of mineral salts, i.e. which suffered *mineral starvation*, lost their appetite, refused food, lost weight, and finally died.

The organism's need for an uninterrupted supply of salts is accounted for by its continuous loss of them in urine, sweat, and faeces.

The physiological role of the different electrolytes is diverse and differs with the mineral. Thus, calcium and phosphorus ions are needed for the formation of bone tissue. Calcium ions are involved in excitation-contraction coupling in a muscle; sodium and potassium ions are essential for the production of bioelectrical potentials. Phosphorus ions occur as residues of phosphoric acid, as constituents of energy-rich compounds (adenosine triphosphoric and creatine phosphoric acids, etc.), and as constituents of phosphatides and phosphoproteins, which are highly important in the activity of the nervous system and in metabolism.

Certain chemical elements that enter into the composition of the organism in extremely small quantities (and are known as micro-elements or trace elements for that reason), e.g. zinc and cobalt, take part in the synthesis of complex organic compounds of great physiological importance.

Calcium, phosphorus, potassium, sulphur, sodium, and chloride occur in relatively large quantities in the organism. Magnesium, iron, and iodine are present in relatively small quantities, and silicon, fluorine, copper, cobalt, manganese, bromine, zinc, arsenic, and aluminium in minimal amounts.

Iodine (its total content in the body of an adult is about 0.03 gramme) is required for synthesis of thyroxine, the hormone of the thyroid gland (p.373).

Iron, the content of which in the body does not exceed three to five grammes, is extraordinarily important, being concerned in oxidizing processes and with the transport of oxygen by the blood. Zinc is a constituent of the enzyme carbonic anhydrase (p.186), and is concerned in the formation of insulin (p.381). Cobalt is a constituent of vitamin B<sub>12</sub>, which is required for blood formation.

#### METABOLISM OF MINERAL SALTS

When minerals are supplied in excess they may be stored in various organs. With an excess supply of sodium chloride, for example, its

content in the subcutaneous cellular tissue rises sharply; with a diet poor in sodium chloride and during starvation, the stored mineral is mobilized and its content in the subcutaneous tissue and other organs falls. The subcutaneous cellular tissue is a *depot for sodium* and *chloride* in the body. Other elements may also be accumulated in various organs, iron, for instance, in the liver, calcium and phosphorus in the bones, and potassium in the muscles. The reserves are mobilized when the organism suffers a deficiency in the supply of these elements. Thus, the bones lose calcium and phosphorus in starvation or with deficient assimilation of calcium. Similarly calcium is mobilized from the bones of a pregnant woman because the foetus requires calcium for its body.

The conventional mixed diet provides the human organism with an adequate amount of mineral salts, with the exception of sodium chloride, which has to be added to food during its preparation. For that reason, the mineral composition of diet needs no special consideration here.

That is not so, however, with respect to the diet of a growing organism which has a particular demand for a great number of minerals. A child requires an adequate supply of calcium and phosphorus in its food for the growth of its bones and the development of its nervous tissue. In addition the child's organism retains sodium, potassium, magnesium, and chloride, an increase of body weight by one kilogram, for example, involving the retention of one gramme of sodium. The richest sources of minerals for a growing organism are milk, eggs, meat, vegetables, and fruit.

The state of the mineral metabolism may be gauged accurately by studying the balance of mineral salts, which is done by determining the amounts of this or that element taken into the organism in food and excreted in urine, faeces, and sweat. Sodium, chloride, potassium, and phosphorus ions are mainly eliminated in the urine, and iron, calcium, and magnesium ions in the faeces (calcium and magnesium may also be excreted in the urine).

With profuse sweating estimates of the balance of minerals are frequently inaccurate because of the difficulties encountered in establishing the amount of salts in the sweat.

**Sodium metabolism.** Sodium mainly enters the body as sodium chloride. The usual daily intake is around four or five grammes, which corresponds to 10.0 to 12.5 grammes of common salt. The organism's requirements, however, can be considerably curtailed. If the amount supplied to the body is reduced to 2.0 to 2.5 grammes, a negative sodium balance will be encountered in the first two days, then its elimination will decline and equilibrium will be attained.

Copious introduction of sodium salts is attended with toxic phenomena. Children may suffer a rise in temperature, a condition known as *salt fever*; the increase in temperature is associated with

stimulation of metabolism. The introduction of nine grammes of sodium increases the metabolism of an adult by 20 per cent.

Up to 45 per cent of the sodium intake is eliminated in the urine and slight quantities in the sweat; with a rise in the environmental temperature, however, sodium losses in the sweat can be significant. It should be noted here that the drinking of a hypertonic NaCl solution in hot surroundings sharply reduces sweating and loss of water by the organism; and there are indications that ten or fifteen grammes of sodium chloride taken before starting on a long route march in hot weather, or when working in 'hot' shops, has a favourable effect.

**Potassium metabolism.** The human body receives two or three grammes of potassium daily in a mixed diet. There is a marked increase if the diet includes vegetables, particularly potatoes. A low potassium content in the blood (*hypokalaemia*) is sometimes encountered owing to the effect of certain drugs which cause elimination of potassium in the urine. Hypokalaemia can lead to disturbances in the contractile activity of the myocardium.

**Calcium metabolism.** Calcium ions influence many enzyme reactions, and play an important role in the process of blood coagulation. They are also concerned in the activity of the muscular and nervous systems.

The daily calcium requirement of an adult is between 0.6 and 0.8 gramme, but the diet must contain much more than that because its carbonates and phosphates are poorly absorbed, so that a negative calcium balance may be encountered even when three or four grammes are available in the daily diet. Thirty grammes of calcium are deposited in the organism during the embryonal development of the foetus, which accounts for the increased calcium requirements of the maternal organism during pregnancy.

Calcium is required for building bones, in which it is deposited in the form of a binary salt  $\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaCO}_3$ , but only if the organism is adequately provided with phosphorus. Calcium and phosphorus occur in optimal proportions in milk.

The amount of calcium in the bones is a thousand times that in the blood plasma. The bones serve as the calcium depot of the organism; a distinctive feature of that is the continuous renewal of the calcium stored in them, which is due to the continuous reconstruction of the bone structure and to the growth of new bone tissue. The activity of one group of bone cells, the osteoclasts, results in the destruction of bone substance; the calcium so liberated enters the blood. Through the activity of another group of bone cells, the osteoblasts, an opposite process takes place simultaneously; the bone tissue destroyed is replaced by new tissue formed with calcium obtained from the blood. In that way, an exchange of calcium between bones and blood occurs continuously in the organism.

In certain cases calcium and phosphorus cannot be deposited in normal amounts, even though their supply is adequate; for instance, disorders of calcium metabolism and excess elimination of calcium in the urine and faeces are encountered in rickets, which is caused by deficiency of vitamin D (p.306), and in tetany which results from impairment of secretion of the parathyroid hormone (p.376).

**Iron metabolism.** Almost the entire iron content of the body occurs in the form of various organic compounds that form complex combinations with proteins, and only a small quantity is ionized. Iron is a constituent of haemoglobin and myoglobin, of the enzymes catalase and peroxydase, and of cytochrome, substances that are all concerned with the transport of oxygen and with oxidation processes. Of the other iron-protein combinations we shall mention only *transferrin*, a protein that carries iron in the blood stream, and *ferritin*, a protein present in the liver and spleen. The iron of ferritin is a reserve drawn on for haeme synthesis.

Iron is mainly absorbed in the upper part of the duodenum. Experiments in adding labelled radioactive iron to food of normal dogs have demonstrated that it is poorly absorbed; it is actively absorbed, however, following loss of blood, and its presence may be observed in ferritin and haemoglobin within a few hours.

The daily iron requirement of an adult human is between ten and thirty milligrams. It is particularly required by a growing organism and during pregnancy.

**Chloride metabolism.** Chloride is mainly deposited in the organisms as sodium chloride. With a copious intake of chloride one-third of the organism's sodium chloride content may be found in the skin. For that reason, the skin may be considered the main depot of chloride.

Chloride is continuously eliminated in urine and faeces, and in small quantities in sweat. Excretion in sweat increases sharply with a high external temperature.

**Phosphorus metabolism.** Phosphorus is involved in the intermediary metabolism of many organic substances. Phosphorylation plays a particularly important part in carbohydrate metabolism, and in the chemism of muscular contraction. Phosphorus is a constituent of the high-energy compounds that are vital to the chemical dynamics and activity of the organism.

Phosphorus is assimilated in the form of sodium and potassium salts, and in easily absorbable phosphorus-containing esters. It is excreted by the kidneys and the intestine. The deposition of phosphorus in the bones is of the greatest importance.

Daily requirement of phosphorus are between one and two grammes. Most of its intake is deposited in the bones and muscles. Four hours after a radioactive isotope of phosphorus is introduced

into the organism, 48 per cent of it is found in the bones and 25 per cent in the muscles.

#### EXCHANGE OF WATER

The water present in the body does not occur in its chemically pure form but either contains dissolved crystalloids or is combined in colloids. Three types of water are distinguished in the organism: 1) the *free water* of the intra- and extracellular fluids, which serves as a solvent of inorganic and organic compounds; 2) *bound water*, which is a constituent of colloids and is responsible for their swelling; 3) *constitutional* or *intramolecular water*, which forms part of the molecule of protein, fat, and carbohydrate, and is liberated when they are oxidized.

The volumes of free and bound water can be established by introducing labelled water (deuterium oxide — D<sub>2</sub>O) into the blood stream. The method has revealed that the body of an adult male contains 61 per cent of water, and that of an adult female, 51 per cent. The water content of a newborn child is much higher, 80 per cent. Water content per unit of weight varies with the organ or tissue, being lowest in the bones (22 per cent) and adipose tissue (30 per cent). The water content of the muscles is 70 per cent of their weight and of the internal organs 76 to 86 per cent. Blood has the highest and most constant water content (92 per cent). When a large volume of water is injected into the blood, its content there does not rise, as it does in the tissues. Similarly, when the organism loses water, there is only a slight decrease in its amount in the blood, while the tissues suffer marked water loss. The tissues, the subcutaneous cellular tissue in particular, serve as water depots for the organism.

At the ordinary temperature and humidity of the environment, the daily water balance in an adult is between 2.2 and 2.8 litres. The organism loses, on average, 1.5 litres of water in the urine, 400 to 600 millilitres in sweat, 350 to 400 millilitres in exhaled air, and 100 to 150 millilitres in the faeces. That loss is compensated by the water drunk (1.5 litres on the average), the water included in food (600 to 900 millilitres on average), and the water formed as a result of oxidation processes (300 to 400 millilitres on average).

The daily water balance may vary within wide limits. Requirements may increase with high temperature or from disorders in the control of water exchange, owing to the high water loss. The character of the diet also has a marked influence; it is well known that the eating of salty food is followed by an increased requirement for water and a feeling of thirst.

#### CONTROL OF WATER-SALT EXCHANGE

The vitally essential constancy of the osmotic pressure of the internal environment of the organism, which is determined by water

and salt content, is maintained by the control of their intake and excretion. The expression of the need for water, which governs the amount of it drunk, is thirst (p.276), that for salts is the so-called salt appetite that is seen in animals which eagerly take in relatively large quantities of salt following a lengthy salt-free diet or, on the contrary, refuse salty food when they have an excess of salt in their organism. The elimination of water and salts is controlled by nervous and humoral influences exerted on the kidneys and sweat glands.

*Vasopressin* (p.406), the hormone secreted by the posterior lobe of the pituitary gland, and *mineralocorticoids* (p.387), hormones of the adrenal cortex, are of major importance in controlling water-salt exchange. Vasopressin inhibits the excretion of water by the kidneys, while the mineralocorticoids cause retention of sodium, an increase in tissue extracellular fluid (which may be attended with *oedema*), and an increase in the elimination of potassium from the organism.

The nerve centre responsible for control of water-salt exchange is located in the diencephalon, in the hypothalamus where special osmoreceptor nerve cells sensitive to changes in electrolyte concentration are located. Their stimulation produces reflex reactions which can restore disturbed constancy of the osmotic pressure of the blood (p.350).

## VITAMINS

Vitamins are organic substances of various chemical nature that are not proteins, fats, or carbohydrates, or their breakdown products, and are necessary for the nutrition of man and animals. They exert a powerful and, to a certain extent, specific influence on the growth, metabolism and physiological state of the organism. Vitamins fulfil various catalytic functions and are required in negligible quantities compared to other nutrients. A vitamin is a definite substance that must be supplied to the animal organism in its food either because it cannot be formed in the organism at all or is formed in amounts that do not meet its physiological requirements. The main sources of vitamins are plants in which either the vitamins themselves are synthesized or substances from which they are formed in the organism, i.e. *provitamins*, are produced. Man obtains vitamins in foods of vegetable and animal origin. Their presence in the latter is due to the fact that vitamins that are obtained from the diet or are synthesized from provitamins can be stored in certain animal organs.

Man requires some sixteen to eighteen vitamins, most of which must be obtained in food. Some of them are synthesized by the

intestinal bacterial flora and absorbed, which is why the organism suffers no deficiency even when those vitamins are lacking in the diet.

The various vitamins have nothing in common, either in regard to their chemical structure or in their biological effect. Some are sources for the production of the active, or *prosthetic, groups of enzyme* in the organism, a process sometimes attended by phosphorylation of the vitamins. An active group containing a definite vitamin combines with a protein which then acquires the properties of an enzyme. The discovery of those facts explained, first, the mechanism by which vitamins influence metabolic processes, and second, the reason why vitamins are required by the body in extremely small quantites, fractions of a milligram as a rule.

The absence of most vitamins from the diet causes death after a certain time, while a deficiency gives rise to various diseases.

Vitamins were discovered by N.I. Lunin who showed in 1881 that the normal physiological state of the animal organism could be maintained only with a diet that contained, apart from proteins, fats, carbohydrates, mineral salts, and water, certain other nutrients the character of which was not then known. His conclusion was based on the results of experiments in which one group of mice was kept on milk, while another group was given an artificial nutrient mixture of sugar, fat, milk protein (casein), the salts contained in milk, and water. The mice of the first group developed normally, while those of the second group died.

Sixteen years after Lunin's work, Eijkman, a doctor working in Indonesia, reported that accessory nutrient factors of some kind were required by the organism. He had observed that fowls fed polished rice (i.e. rice grains freed of their outer coat) for a long time sickened and died. The condition resembled beri-beri, a disease then widespread in Japan, China, and certain other countries. The addition of rice bran to the fowls' diet had cured them of the disease.

A broad study of vitamins was started in the period between 1910 and 1912.

The term "vitamines" was suggested in 1912 by Funk, who had concluded that they were substances indispensable to life (L. *vita* life; vitamins, vital amines). It became clear later that the presence of an amino group is by no means characteristic, since many of these substances have no nitrogen, but the term shortened to "vitamins" has become firmly established in science.

The absence of one vitamin or another from the diet gives rise to a pathological condition known as *avitaminosis*, and deficiency to *hypovitaminosis*. The various types of these conditions (for example, scurvy, rickets, pellagra, polyneuritis, etc.) differ markedly in their clinical picture and are entirely different diseases. Each can be pre-

vented or cured by the introduction of the corresponding vitamin into the organism.

Many of the phenomena encountered in avitaminosis probably result from some disturbance in the formation of certain enzymes owing to the absence of vitamins in the diet.

Most avitaminoses encountered in man can be induced in experimental animals, but susceptibility varies from species to species. Attempts to reproduce scurvy in birds, for instance, have proved fruitless, while guinea pigs acquire the disease easily. For that reason, animals are chosen, when studying one avitaminosis or another, that react readily to lack of the given vitamin in their diet.

To reproduce avitaminosis or hypovitaminosis experimentally, animals are kept on artificially prepared nutrient mixtures or foods that are devoid of definite vitamins but contain proteins, fats, carbohydrates, mineral salts, and water in adequate quantities.

Avitaminosis or hypovitaminosis can occur even when vitamins are supplied in the diet, if their absorption (in diseases of the alimentary tract) or utilization in the organism are impaired—a type of condition known as secondary.

Hypovitaminosis may be encountered with a normal diet when requirements of vitamins are increased, for example in pregnancy, growth, infections, or when antibiotics are prescribed.

Vitamins are designated by letters of the alphabet and by chemical or physiological names (the physiological name given depends upon the character of the effect produced by the vitamin). The alphabetical designation was introduced when the first substances of the vitamin group had only been discovered and their chemical nature was still unknown.

All vitamins are divided into two major groups: 1) those soluble in water, and 2) those soluble in fats. The group of *water-soluble* vitamins includes the numerous members of the vitamin B complex, vitamin C (ascorbic acid), and vitamin P.

The vitamin B group includes vitamin B<sub>1</sub> (thiamine), vitamin B<sub>2</sub> (riboflavin), vitamin B<sub>6</sub> (pyridoxine), vitamin B<sub>12</sub> (cyanocobalamin), vitamin P-P (nicotinamide), pantothenic acid, biotin, folic acid, choline, and a number of other substances.

The group of *fat-soluble vitamins* consists of vitamins A<sub>1</sub> and A<sub>2</sub> (retinol and dehydroretinol), vitamin D (ergocalciferol), vitamin E (tocopherol), vitamin K (phylloquinone).

Many vitamins are rapidly broken down in the human organism and are not stored in large quantities, so that they must be constantly obtained from food. That is particularly true with regard to vitamins A, D, B<sub>1</sub>, B<sub>2</sub>, P-P, and C.

The daily vitamin requirements of the organism are shown in the following table:

	Vitamins						International Units*
	A	B <sub>1</sub>	B <sub>2</sub>	C	P-P	D	
	milligrams						
Adults	1	2-3	2	50-75	12-20	up to 100	
Women during pregnancy and lactation	2-2.5	3	2	75-100	18-20	500-1000	
Children under 7	1	1	2	35	12	500-1000	
Children over 7	1	1.5-2	2	50	12	500-1000	

\* One International Unit corresponds to 0.000025 milligram of pure vitamin D.

#### VITAMIN B<sub>1</sub> (THIAMINE).

Deficiency of vitamin B<sub>1</sub> in man causes the avitaminosis known as *beri-beri* or *polyneuritis*, which is marked by impairment of the nervous system resulting in disturbances of movement, particularly of gait and in paralysis.

An individual suffering from beri-beri drags his feet with an effort and his gait resembles that of a person in shackles. Onset of the disease is attended with symptoms of early fatigue, loss of appetite, palpitations, and pain in the legs. Gradually (fairly rapidly in some cases) severe disturbances of sensation and gait or paralysis of the arms and legs develop, the patient becomes extremely exhausted, and death occurs from paralysis of the respiratory muscles. In other cases development of the disease may be marked by severe circulatory disorders, oedema, and muscular atrophy. Observation of patients has revealed that the disease develops after 30 to 90 days of a diet lacking vitamin B<sub>1</sub>.

B<sub>1</sub> avitaminosis can be induced in birds, albino rats, and dogs by feeding them either polished rice or unpolished rice previously treated for two or three hours in an autoclave at 120°C. B<sub>1</sub> avitaminosis in animals is also attended by convulsions, disturbances of movements, and paralyses.

The metabolic disorders encountered are associated with the fact that the active group of the enzymes carboxylase and dehydrase is formed from vitamin B<sub>1</sub> (thiamine) in the organism. Carboxylase catalyses the breakdown of pyruvic acid with the formation of acet-aldehyde; dehydrase promotes the breakdown of pyruvic acid to acetic acid. Deficiency or absence of thiamine inhibits the formation of these enzymes and so disturbs metabolism in various organs, including the nervous system. The metabolism of amino acids, the

resynthesis of carbohydrates, and the formation of acetylcholine in the nervous system are impaired in  $B_1$  avitaminosis.

Brewer's yeast, rice bran, whole wheat flour, oatmeal, walnuts, beef liver, egg yolk, and beans have the richest sources of vitamin  $B_1$ .

Thiamine is destroyed when foods containing it are heated to 120°C.

Vitamin  $B_1$ , or thiamine, has been synthesized and is produced industrially, which permits the practice of artificial vitaminization of food, i.e. the addition of preparations of this vitamin to bread, for example, and other foods.

Since no significant amounts of thiamine are stored in the body, it must be supplied regularly in the diet. If an adult obtains only half of the daily required quantity over a period of five or six days, symptoms of hypovitaminosis appear, i.e. lassitude, fatigue, palpitations, pain in the region of the heart, a tendency to cramps in the extremities, and tenderness of the skin. All these symptoms are relieved in a few hours after taking a few milligrams of vitamin  $B_1$ .

#### VITAMIN $B_2$ (RIBOFLAVIN)

Lack of vitamin  $B_2$  in the diet results in lesions of the skin and eyes and in retarded growth in young animals. The vitamin is a combination of flavin and a pentatomic alcohol ribitol, and is known as *riboflavin*. It has been isolated in a chemically pure form from food-stuffs and synthesized. Riboflavin preparations stimulate growth in animals kept on a diet free of vitamin  $B_2$ .

Riboflavin oxidizes and reduces easily, its oxidation-reduction properties being readily reversible. In the form of its phosphorus ester riboflavin is a constituent of the coenzyme of a number of enzymes concerned in oxidation-reduction processes. This group of flavin enzymes includes the *yellow respiratory enzyme* discovered by Warburg in yeast; *amino acid oxidase*, which is concerned in the oxidation of at least thirteen different amino acids; enzymes responsible for dehydrogenation, i.e. *diaphorase* and *cytochrome reductase*; *xanthine oxidase* which catalyses the oxidation of purines; enzymes that contribute to the oxidation of aldehydes, including *glucose oxidase*.

The animal organism does not synthesize riboflavin, so that it has to be obtained in food. Its reserves in the organism are not great because a large intake is followed by an increase in its elimination. During lactation riboflavin obtained from food enters the milk and satisfies the requirements of the offspring. The daily requirement of man is about two milligrams.

Yeast, tomatoes, spinach, cabbage, cereal grains, certain animal organs (kidneys, liver, brains), and eggs are rich in riboflavin.

Riboflavin deficiency is rarely encountered in man because the substance occurs widely in animal and vegetable tissues. Avitamin-

osis is marked by inflammatory lesions of the lip mucosa and the appearance of fissures which become encrusted. Involvement of the skin and cornea are also encountered, severe cases terminating in corneal opacification.

#### ANTIPELLAGRA· FACTOR (NICOTINAMIDE – VITAMIN P-P)

Nicotinic acid and its amide are vitamins lack of which gives rise to a severe disease in man, *pellagra*. Hence they are also known as the P-P factor (pellagra preventive). Pellagra is characterized in man by the three D's, three groups of symptoms each beginning with the letter D: *dermatitis* (skin involvement), *diarrhoea*, and *dementia* (mental deterioration).

Pellagra is cured by small doses of nicotinic acid and its derivatives, of which nicotinamide is the most active.

Nicotinamide takes part in many metabolic processes because it is a component of two important coenzymes that catalyse about forty different chemical reactions occurring during carbohydrate breakdown and oxidation-reduction processes.

Nicotinic acid and nicotinamide can be synthesized from tryptophane in the organisms of many mammals; therefore pellagra does not develop with a diet lacking the P-P factor but including proteins rich in tryptophane.

#### VITAMIN B<sub>6</sub> (PYRIDOXINE)

Vitamin B<sub>6</sub> comprises a group of related compounds, the most important of which is *pyridoxine*, which is converted in the organism into pyridoxal phosphate, the active group of a number of enzymes.

Braunstein and others have shown that pyridoxine and its derivatives take part in the metabolism of amino acids, i.e. in the transfer of the amino group from one amino acid to another (transamination reaction), and in amino acid decarboxylation.

Skin lesions (dermatitis), changes in blood composition (anaemia and a fall in lymphocyte count), and convulsions were encountered when pyridoxine was missing from the diet of animals. Individual cases of pyridoxine avitaminosis in man have been reported, marked by anaemia and convulsions.

Pyridoxine is synthesized by the intestinal bacteria, and man does not usually suffer a deficiency in this vitamin when it is lacking in the diet. Symptoms of pyridoxine avitaminosis may occur, however, if the growth of intestinal bacteria is suppressed by the powerful modern antibiotics.

The daily requirement in pyridoxine in man is between two and four milligrams. Yeast, liver, kidneys, and muscle are rich in this vitamin.

### PANTOTHENIC ACID

Pantothenic acid is important for the growth of all cells and is very widely distributed (hence its name from the Greek for all-sided). Lack of the acid in experimental animals results in retarded growth, loss of weight, pathological changes in the skin, greying of the fur, anaemia, and involvement of the adrenal glands; convulsions terminating in death are encountered in dogs.

Pantothenic acid is a component of the acetyl coenzyme A which is concerned in a number of chemical transformations occurring in the organism.

The daily requirement of man is between five and ten milligrams, which is fully provided in the normal mixed diet.

### BIOTIN (VITAMIN H)

Skin lesions, disturbances of the appetite, weakness, and somnolence are encountered in man with biotin deficiency.

Biotin is a component of the active group of the enzymes that are concerned with the carboxylation of dicarboxylic and tricarboxylic acids (the addition of carbon dioxide). Biotin avitaminosis cannot be induced in mammals by excluding biotin from their diet because the vitamin is synthesized by the bacteria in the intestine. It has been established that, because of the absorption of biotin formed in the intestine, the amount eliminated in the urine exceeds its content in the diet. Biotin avitaminosis can develop, however, if raw egg white enters the intestine with food. The explanation is that *avidin*, an albumin present in the white of hen's eggs, binds biotin forming an insoluble complex that cannot be broken down by the digestive enzymes. The absorption of biotin is thus impaired, which gives rise to avitaminosis.

Biotin deficiency may be encountered in man following large doses of sulphonamides that suppress its synthesis by the bacterial flora of the intestines.

### FOLIC ACID

Folic acid deficiency leads to disturbances of blood formation, retarded maturation of blood cells in the bone marrow, and delayed release of cells into the blood. Anaemia and leucopenia (reduced leucocyte count) occur as a result. This avitaminosis has been induced experimentally in guinea pigs, dogs, and monkeys. The human organism obtains folic acid in its food and by its bacterial synthesis in the intestine. Deficiency is therefore a rare occurrence. Hypovitaminosis may be encountered, nonetheless, if the growth of intestinal bacteria is suppressed by large doses of certain drugs and the diet is poor in folic acid.

### VITAMIN B<sub>12</sub> (CYANOCOBALAMINE)

Vitamin B<sub>12</sub> is a complex cobalt-containing compound of the porphyrin group. It is concerned with the metabolism of a number of substances, particularly the nucleic acids, and is most important for normal blood formation. B<sub>12</sub> avitaminosis is manifested by malignant anaemia characterized by disturbances of erythropoiesis, i.e. the formation of erythrocytes, and by disorders in nervous activity. The introduction of vitamin B<sub>12</sub> exerts a powerful therapeutic effect, restoring the haemopoietic function of the bone marrow. A dose of thousandths of a milligram is sufficient to produce this effect. A pure preparation of the vitamin has a therapeutic effect in malignant anaemia only when it is injected subcutaneously or into the blood, because these patients cannot absorb it from the intestine. The organism can assimilate vitamin B<sub>12</sub> only when the gastric glands secrete a mucoprotein, the presence of which was revealed several decades ago and which was called intrinsic or Castle's factor. Formation of the factor is impaired in malignant anaemia so that the vitamin supplied in food is not assimilated.

Thus, the B<sub>12</sub> avitaminosis occurring in the form of malignant anaemia is secondary in origin since it is caused not by a deficiency of the vitamin in the diet, but by impairment of its entry into the organism from the alimentary tract. Liver and kidneys are the richest sources of vitamin B<sub>12</sub>.

### VITAMIN B<sub>15</sub> (PANGAMIC ACID)

Pangamic acid is a nitrogenous derivative of a complex ester of gluconic and acetic acids containing four methyl groups. It has been found to be present in the seeds of many plants (hence its name, from Greek *pan* all, *gamy* seed). The acid has also been isolated from the blood and liver of horses. Pangamic acid heightens the utilization of oxygen by the cells and promotes the oxidation of alcohol in the organism. The compound is used to treat certain cardiac and vascular diseases.

### CHOLINE

The formation of choline in the organism, or its presence in ready form in food, is necessary for normal fat metabolism and phospholipid synthesis.

Fatty infiltration of the liver occurs in animals if choline, or phospholipids that contain it (lecithin, for example), are lacking in the diet. The condition is quickly cured by adding choline to the ration, the amount of fatty acids in the liver being reduced. That is attributed to the synthesis of phospholipids in the liver in the presence of choline, and their rapid transfer to other organs. Choline

can be synthesized in the organism from the amino acid methionine. Fatty infiltration of the liver is not encountered if the organism receives large amounts of methionine, even when choline is absent from the diet. Choline is also involved in the formation of acetyl-choline.

#### VITAMIN C (ASCORBIC ACID)

A diet that is completely lacking, or poor in, vitamin C causes scurvy in man.

*C avitaminosis*, or *scurvy*, is a disease marked by spongy and bleeding gums, teeth that loosen and fall out, haemorrhages in the muscles, skin, and joints, increased porosity and fragility of the bones that may lead to fractures, and the progression of general lassitude, exhaustion, and disturbances in the nervous system.

Prolonged deprivation of vitamin C results in death either from exhaustion or from concomitant infectious diseases, which is accounted for by the fact that *C avitaminosis* is characterized by low body resistance to infections.

Scurvy becomes widespread when difficulties are encountered in providing populations with food, i.e. with bad harvest and during wars when the diet is poor in fresh vegetables and fruit. The disease used to be common among seamen on long voyages and people wintering in the Far North when supplies of fresh meat and vegetables were exhausted. The importance of food in the development of the disease was pointed out long ago from those facts.

*C hypovitaminosis*, i.e. a relative deficiency in the supply of vitamin C, is encountered more frequently than *C avitaminosis*. Its symptoms are lassitude, early fatigue, weakness of the muscles, dizziness, bleeding of the gums, and lowered resistance to infectious diseases.

Vitamin C has been isolated in a chemically pure form, synthesized, and produced by the pharmaceutical industry. It is otherwise known as *ascorbic acid*, i.e. the substance that prevents scurvy.

Ascorbic acid takes part in the oxidation-reduction processes occurring in the cells and activates the protein-splitting enzymes.

The daily requirements of an adult human range between 50 and 75 milligrams, increasing with strenuous muscular work, particularly in hot shops, with many serious illnesses, and with pregnancy.

Vitamin C is synthesized in the organisms of many animals, but not in man, monkeys, and guinea pigs, which have to be supplied with it in the diet.

Ascorbic acid is present in many foodstuffs; cabbage, tomatoes, lemons, oranges, black currants, pepper, fennel, the germinating seeds of cereals, carrots, beetroot, string beans, and potatoes are rich sources, while rose hips and unripe walnuts are extremely rich.

#### VITAMIN P (PERMEABILITY VITAMIN)

The term vitamin P embraces a group of plant pigments or flavonoids deficiency of which increases the permeability of the capillaries and makes their walls more fragile, leading to haemorrhages into the skin and other organs. Certain symptoms of scurvy are caused by P avitaminosis. It has been shown that three different substances, isolated from lemon rind (hesperidin), from buckwheat leaves (rutin), and from the green leaves of the tea plant possess the action of vitamin P. Their introduction into the body lowers the permeability of the capillaries and has a therapeutic effect.

#### VITAMIN A (RETINOL, AXEROPHTHOL)

Vitamin A is a fat-soluble substance formed in the intestine and liver of man and animals that eat vegetable foods. Its source is *carotene*, a pigment synthesized by many plants. The carotene molecule is split by the action of the enzyme carotenase into two molecules of vitamin A. The chemical structure of the vitamin has been revealed and it has been named *retinol*. *Dehydroretinol* also possesses the properties of vitamin A.

Young animals kept on a diet of artificial food mixtures containing no vitamin A cease to grow and develop corneal lesions.

Lack of vitamin A in the diet of man has an effect on the epithelial tissue; the epithelium of the conjunctiva of the eye becomes dry and keratotic (xerophthalmia), and the cornea becomes opaque and soft (keratomalacia). In advanced cases leucoma persists even after treatment with vitamin A. Changes in the epithelium, keratinization in particular, also occur in other organs, in the skin, respiratory passages, bladder, ureters, and intestine.

The earliest symptom of vitamin A deficiency is impairment of twilight vision, the condition known as *night-blindness*, i. e. inability to see in dim light. It is due to the fact that the amount of visual purple in the retinal rods decreases with A avitaminosis or hypovitaminosis. Visual purple is a compound formed from a vitamin A derivative and the protein opsin (vol.II, Chapter 14).

Because of the importance of vitamin A to normal functioning of the rods, individuals whose occupation involves straining of the eyes in twilight or at night require it in large quantities.

Vitamin A is present in animal fats, fish-liver oil, butter, milk, egg yolk, liver, kidneys, and roe. Carrots, spinach, apricots, paprika, nettles, and lucerne are rich sources of carotene.

Vitamin A is stored in the liver, which serves as its depot. The daily requirement of a human adult is around one milligram.

#### VITAMIN D (ERGOCALCIFEROL, ANTIRACHITIC VITAMIN)

Deficiency of vitamin D in a child's diet leads to the development of the disease known as *rickets*. It is characterized by changes in the

skeleton (the bones of the legs, chest, and spinal column) consisting in inadequate calcification of the cartilaginous and newly formed bone tissues, which are most pronounced at the junction of the diaphysis and the epiphysis. Abnormal softness and deformities of the bones are encountered. The deformities of the leg bones observed in sick children are a typical symptom of rickets.

Bone calcium content is sharply reduced in rickets (by 66.7 to 71.5 per cent in severe cases). Phosphorus content is also somewhat lower.

Vitamin D deficiency in adults produces softening of the bones (osteomalacia) due to lack of calcium salts arising from their deficient deposition and excess elimination.

A negative calcium balance is encountered in D avitaminosis, i. e. its output exceeds its intake.

Observation of patients and experiments on animals have established that vitamin D is essential for the assimilation of calcium and for phosphorus-calcium metabolism.

Studies of the chemical structure of vitamin D have revealed the existence of a number of chemically related substances all capable of an antirachitic effect. These compounds, known as vitamins D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>, have been obtained by ultraviolet irradiation of the 7-dehydrocholesterol contained in animal fats, and the ergosterol present in vegetable oils. The compounds formed as a result of the photochemical reaction have extremely high antirachitic activity. Thus, vitamin D<sub>2</sub> (or *ergocalciferol*) in a daily dose of  $\frac{1}{40}$  of a microgram (0.025 microgram) prevents rickets in young rats.

Vitamin D can be formed from 7-dehydrocholesterol in the skin in man under the effect of ultraviolet rays, which explains the age-old observation that the incidence of rickets among children is higher in winter than in summer. Exposure to the effect of sunshine or artificial ultraviolet irradiation is a powerful means of preventing and treating rickets.

Fish-liver oil and egg yolk are rich sources of vitamin D.

The daily vitamin D requirements of an infant are between ten and twenty-five micrograms of the crystalline preparation, a dose that protects against rickets and ensures normal calcium metabolism. Adults also require a small supply of the vitamin in their diet.

#### VITAMIN E (TOCOPHEROL, VITAMIN OF REPRODUCTION)

Vitamin E is essential for the processes of reproduction. Without it in the diet normal development of spermatozoa in the testes (spermatogenesis), normal pregnancy and lactation, and viability of the progeny are impossible.

The first half of pregnancy in animals suffering E avitaminosis is usually uneventful, but during the second half the foetus dies and

either undergoes resorption or is aborted. In some cases the progeny die after birth. The foetus suffers more from the lack of vitamin E than the mother. A decrease in the size of the testes and disturbances in the production of the sperm-forming cells are encountered in the males; the spermatozoa lose their motility and are rapidly destroyed. In severe cases the animals display no sexual desire.

The normal state of the reproduction system is restored by introducing vitamin E preparations. In immature animals early sexual maturity is caused by vitamin E, its effect being similar to that of the hormone secreted by the anterior lobe of the pituitary gland. This lobe and the placenta are the richest of all the body structures in vitamin E.

These facts point to a connection between vitamin E and the formation of the gonadotropic hormone in the pituitary gland.

As well as disturbances in the functioning of the reproduction system, involvement of the striated muscles, *muscular dystrophy*, is encountered in E avitaminosis. The condition is marked by degeneration of the muscles resulting in destruction of the myofibrils, and is frequently attended with degenerative phenomena in the spinal cord.

E avitaminosis is a rare occurrence in man because the vitamin is present in many foodstuffs. Cases have been described in the medical literature, nonetheless, in which sterility in women has been cured by increasing the vitamin E content of their diet. It is also possible that certain diseases of the muscular system in man are associated with vitamin E deficiency or with disturbances in the metabolism of the vitamin.

Large amounts of vitamin E are present in lettuce, wheat and maize germ, vegetable oils, and animal tissues. It belongs to the group of vitamins that dissolve in fats.

A number of substances occurring in foodstuffs have been isolated, that are identical in structure and possess the properties of this vitamin. They have been designated alpha-, beta-, and gamma-tocopherol (Gr. *tokos* childbirth, *pherein* to carry).

#### VITAMIN K (PHYLLOQUINONE, ANTIHAEMORRHAGIC FACTOR)

Vitamin K deficiency causes a decrease in the prothrombin content of blood, resulting in disturbances in its coagulation. A tendency to bleeding (*haemorrhages*) is observed with K avitaminosis in consequence.

Vitamin K is required for the synthesis of prothrombin in the liver. Parenteral introduction of vitamin K, i. e. other than by way of the alimentary tract, facilitates this process in avitaminosis, restores the normal content of prothrombin in the blood, increases its coagulation, and so alleviates the tendency to haemorrhages. Hence vitamin K is known as the *antihaemorrhagic vitamin*.

Vitamin K is present in various foodstuffs and is also synthesized by bacteria in the colon. For that reason, K avitaminosis may only be encountered in humans when intestinal absorption of the vitamin is impaired, which occurs if the intestine contains no bile acids (in obstruction of the bile duct for example) since their presence is indispensable for its absorption. K avitaminosis can therefore develop in diseases of the bile passages although adequate quantities of the vitamin are present in the diet.

A tendency to bleeding due to a deficiency in prothrombin, sometimes encountered in newborn infants, is attributed to K avitaminosis. This haemorrhage of the newborn is successfully prevented by prescribing vitamin K to the mother before delivery.

Vitamin K is present in large amounts in spinach, lettuce, cabbage, and carrots. A crystalline compound possessing its properties has been derived from plants, which proved to be a di-derivative of naphthoquinone and was called *phylloquinone*.

A substance formed by bacteria responsible for the putrefaction of fish meal possesses the properties of vitamin K, i.e. causes an anti-haemorrhagic effect. It has also been found to be a derivative of naphthoquinone (*pharnoquinone*). Unlike the preparation derived from plants it was named vitamin K<sub>2</sub>. A number of synthetic naphthoquinone derivatives characterized by the properties of vitamin K were subsequently discovered. Some of them are water-soluble as, for example, the bisulphate derivative of methyl-naphthoquinone discovered by Palladin.

Dicumarol is an antagonist of vitamin K, and inhibits the synthesis of prothrombin in the liver, thus disrupting the coagulation of blood in the organism.

#### TRANSFORMATION OF ENERGY AND TOTAL METABOLISM

##### PRINCIPLES OF RESEARCH IN TOTAL METABOLISM

The intensity of the *total metabolism* and the character of the substances that undergo oxidation in the organism can be judged by the volume of the oxygen intake and of the breakdown products eliminated from the body. For instance, the amount of protein broken down is established from the amount of nitrogen discharged in the urine. The amounts of carbohydrates and fats oxidized are determined by the volume of carbon dioxide eliminated and the volume of oxygen consumed over the same period of time, i.e. by the indices of gas exchange, taking into account that carbon dioxide is produced in the body not only as a result of fat and carbohydrate oxidation, but also as a result of protein oxidation. Having estimated the amount of protein broken down in the organism in 24 hours from the nitrogen output, one can calculate the amount of carbon contained in them (the carbon content of proteins averages 52 per cent). The difference between the total quantity of carbon

in the proteins broken down and the quantity of carbon present in the urine (in which it occurs mainly in the breakdown products of protein) makes it possible to estimate the amount of protein carbon converted into carbon dioxide and the amount of oxygen used up in the process. By subtracting the amount of oxygen expended on protein oxidation from the total amount absorbed by the organism during the period studied one can establish the amount of oxygen utilized to oxidize fats and carbohydrates. Further calculations enable one to determine how much oxygen was used to form both carbohydrates and fats, and thus to estimate the amounts of these substances oxidized in the organism. The calculation is based on the fact that the oxidation of one gramme of carbohydrate and of one gramme of fat requires different amounts of oxygen and releases different quantities of carbon dioxide.

Let us consider an example of those calculations. Suppose that the examined individual has consumed 672.8 litres of oxygen in 24 hours and has lost 628.3 litres of carbon dioxide in the exhaled air, and 13.1 grammes of nitrogen and 7.68 grammes of carbon in the urine within the same period of time. Since one gramme of nitrogen is contained in every 6.25 grammes of protein,  $13.1 \cdot 6.25 = 81.8$  grammes of protein were consequently broken down. That amount of protein contains  $\frac{81.8 \cdot 52}{100} = 42.5$  grammes of carbon.

By subtracting the amount of carbon excreted in the urine from the total amount in the protein broken down, we find how much protein was used to produce carbon dioxide, i. e.  $42.5 - 7.68 = 34.8$  grammes. That amount of carbon yields (according to the carbon-carbon dioxide ratio)  $\frac{34.8 \cdot 44}{12} = 127.6$  grammes of carbon dioxide. The oxidation of 34.8 g of carbon requires (according to the carbon-oxygen weight ratio in carbon dioxide)  $\frac{34.8 \cdot 32}{12} = 90.28$

grammes of oxygen. We must also take into account that 100 g of protein contain 3.439 grammes of hydrogen, which requires a supply of oxygen from the external environment for its oxidation. The 81.8 grammes of protein broken down contain 2.81 g of hydrogen, oxidation of which (with the formation of water) requires 22.48 g of oxygen. Thus,  $90.28 + 22.48 = 112.76$  grammes of oxygen were required to oxidize the proteins in our example.

Since one gramme of carbon dioxide has a volume of 0.5087 litre, and one gramme of oxygen a volume of 0.699 litre at 0° and at an atmospheric pressure of 760 millimetres mercury, it is easy to establish that the carbon dioxide produced from the proteins in our example has a volume of  $127.6 \cdot 0.5087 = 64.9$  litres, and the oxygen used to oxidize the proteins a volume of  $112.76 \cdot 0.699 =$

= 77.8 litres. After having subtracted these amounts from their respective 24-hour intake or output, we can establish the amount of oxygen utilized to oxidize carbohydrates and fats, and the amount of carbon dioxide formed as a result of that process. The corresponding values in our case will be:  $672.8 - 77.8 = 595$  litres of oxygen, and  $628.3 - 64.9 = 563.4$  litres of carbon dioxide.

Further calculations to estimate the amount of oxygen utilized to oxidize carbohydrates and fats and the amounts of carbon dioxide formed in both cases must take into account that while the quantity of oxygen used to oxidize carbohydrates is equal to the quantity of carbon dioxide produced, the ratio of carbon dioxide output to the oxygen intake in fat oxidation is 0.7 (the respiratory quotient, see p.316). The following equations can be drawn up on that basis, in which X designates the volume of oxygen expended to oxidize fats, Y the volume of carbon dioxide produced in the process, A the volume of oxygen expended to oxidize carbohydrates and the equal volume of carbon dioxide produced by carbohydrate combustion in the organism:

$$1) \frac{Y}{X} = 0.7$$

$$2) X + A = 595$$

$$3) Y + A = 563.4$$

Solving these equations we find that 489.6 litres of oxygen were expended to oxidize carbohydrate (A) in our example, and 105.4 litres to oxidize fats (X).

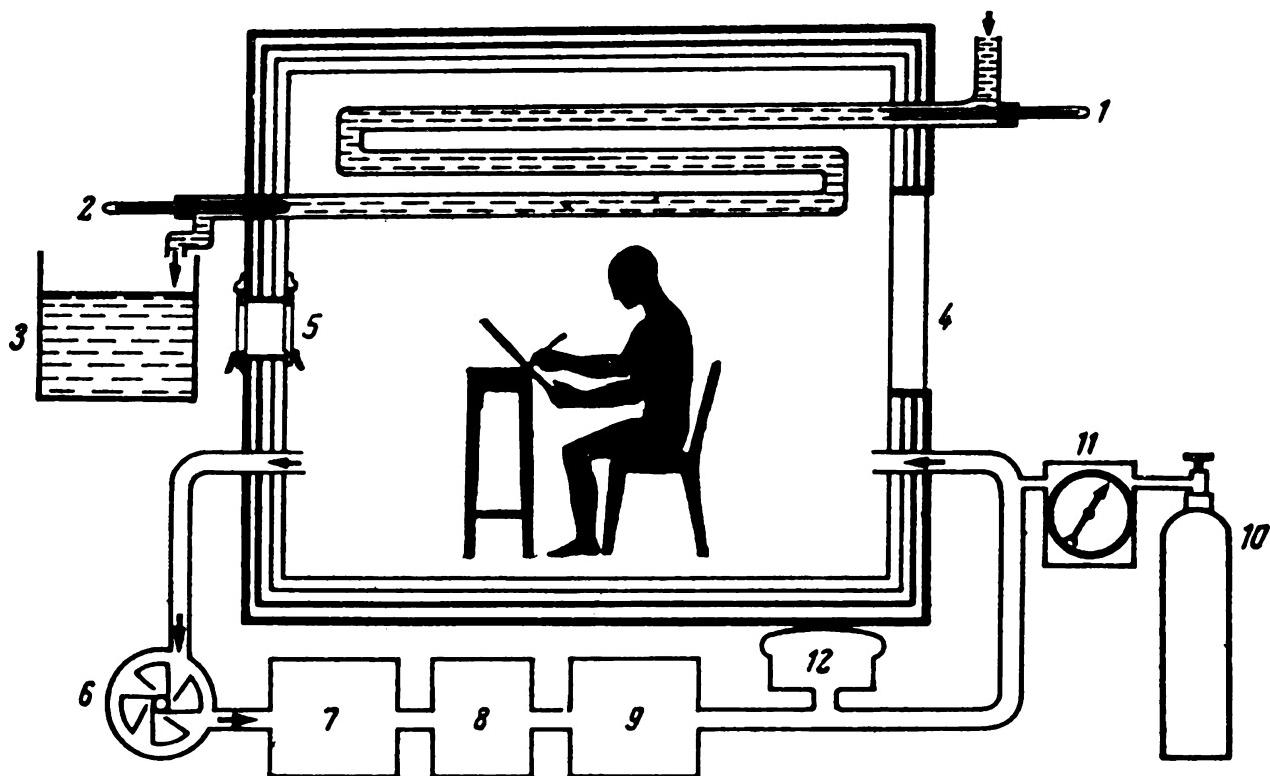
Since the oxidation of one gramme of carbohydrate requires 0.830 litre of oxygen (see p.315), and the oxidation of one gramme of fat, 2.030 litres, we can calculate the amounts of fats and carbohydrates that were broken down in this case during 24 hours, i. e.  $489.6 : 0.830 = 590$  g of carbohydrate and  $105.4 : 2.030 = 51.9$  g of fat.

Thus, determination of the 24-hour intake of oxygen and output of breakdown products, and calculation of the total metabolism show, in our example, that the organism expended 81.8 g of protein, 590 g of carbohydrates, and 51.9 g of fats.

With the total metabolism estimated, one can determine the energy expenditure of the body since the amounts of heat energy in Calories (kilocalories), liberated as a result of the oxidation of one gramme of carbohydrate, protein, or fat is known (p.323).

#### HEAT PRODUCTION (DIRECT CALORIMETRY)

The processes of disassimilation are attended with liberation of energy, i. e. transformation of potential chemical energy into



**FIG. 93. Diagram showing the Atwater-Benedict calorimeter chamber**

The heat produced by the human body heats the water that flows along pipes in the chamber, the temperature being recorded by the thermometers (1 and 2). The amount of water is measured in the vessel (3). Food is served and the excreta removed through the porthole (5). Air is drawn out from the chamber by means of pump (6) and passed through tanks containing sulphuric acid (7 and 9) for the absorption of water and through a tank containing soda lime (8) for the absorption of carbon dioxide. Oxygen is introduced into the chamber from the cylinder (10) through a gas meter (11). The air pressure in the chamber is maintained at a constant level with the aid of a vessel supplied with a rubber valve (12).

kinetic. Most of it is converted into heat and 20 to 25 per cent may be transformed into mechanical energy. The liberation of electrical energy is negligible.

The end result of energy transformation is the production of heat which is given off into the external environment. The mechanical energy released during cardiac contractions and responsible for the movement of the blood, for instance, is expended on overcoming resistance and is transformed into heat energy. The same phenomenon is encountered during the work of the skeletal muscles; the mechanical energy produced during this activity is transformed into heat outside the organism.

The total amount of energy liberated can be determined by the methods of direct or indirect calorimetry and expressed in units of heat (Calories or kilocalories).

*Direct calorimetry* employs special complex apparatus known as *calorimeter chambers*, which absorb the heat. Chambers of this kind for humans and large animals were devised by Pashutin and Likhachev (1893) in Russia and later by Atwater (1899) and Benedict in the USA (Fig. 93).

Calorimetric data can be very precise, as was demonstrated experimentally by Rubner, who determined the energy expenditures

of the body in a chamber, calculated total metabolism, and compared the results. Calculations of heat production on basis of the total metabolism and direct measurement of the heat produced in the chamber differed by no more than 0.5 per cent. In one experiment, for instance, the body of a dog released 2,494 kilocalories during eight days spent in the chamber. Calculations of its heat production from data yielded by study of its total metabolism showed that 2,488 kilocalories were set free in its body. The difference between the two values lies within the limits of the possible measurement error.

The estimation of the energy expenditure of the organism either by direct calorimetry or by calculating total metabolism is extremely complicated, and it is much simpler and more convenient in practice to calculate it by studying the gas exchange, i.e. by indirect calorimetry.

#### GAS EXCHANGE AS AN INDEX OF BODY ENERGETICS (INDIRECT CALORIMETRY)

The organism's sources of energy are oxidation processes which are attended with consumption of oxygen and production of carbon dioxide. Therefore its energy expenditures can be determined by studying the exchange of gases, i.e. from the quantities of oxygen absorbed and carbon dioxide released, a method known as *indirect calorimetry*.

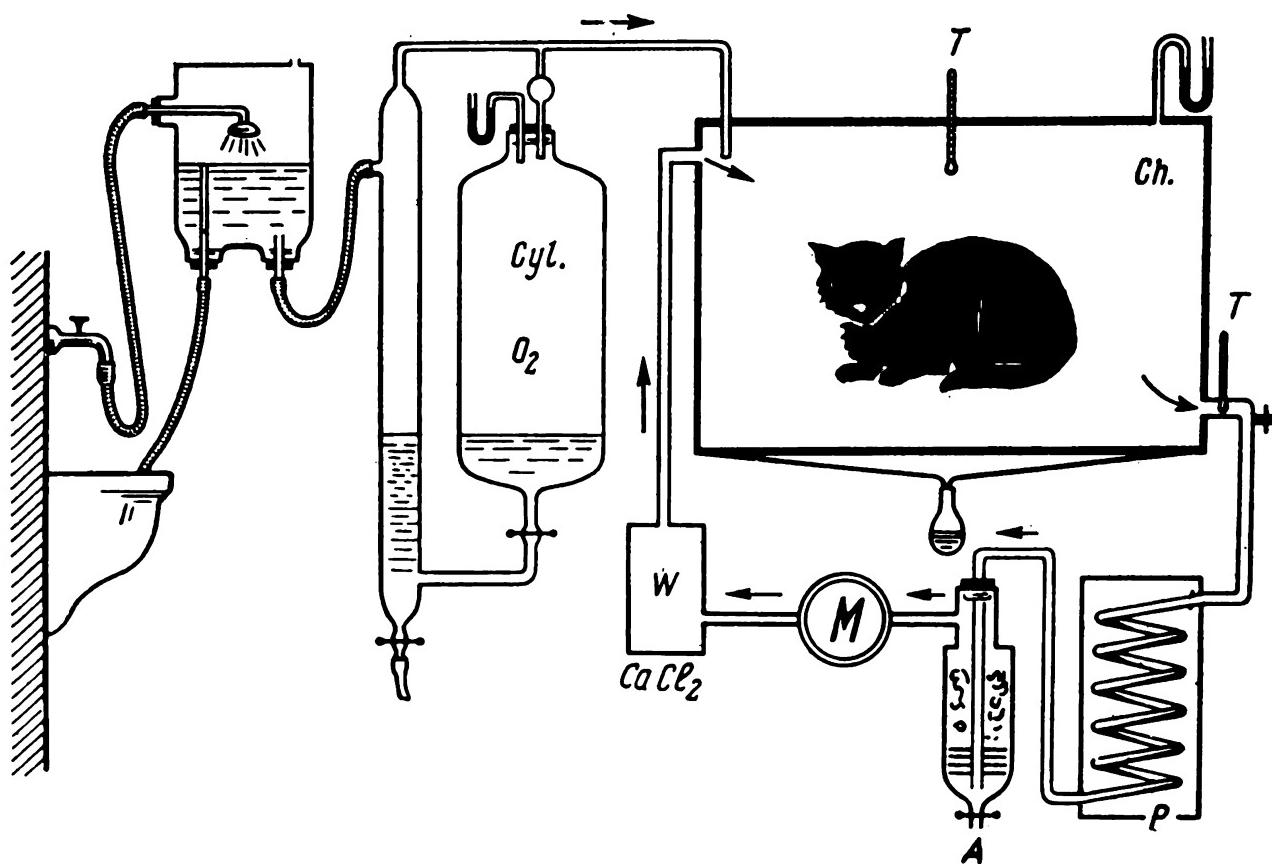
Special *respiration chambers* are used for prolonged studies of gas exchange. Convenient models were devised and described by Pashutin (1886) and later by Shaternikov (Fig. 94).

The respiration chamber makes it possible to investigate gas exchange in man or an animal for 24 hours or longer. Short-period studies on individuals at work, at school, in hospital, etc., employ simpler techniques.

The most widely used technique is that of Douglas and Haldane which employs a face mask or mouthpiece connected to a bag made of airtight material (a Douglas bag) worn on the subject's back (Fig. 95). The mask is fitted with valves so that the subject easily breathes in atmospheric air and exhales it into the Douglas bag.

The exhaled air is collected over a definite time interval (ten to fifteen minutes) and its volume is measured (by measuring the total volume of air in the bag with a meter) and its percentage content of oxygen and carbon dioxide determined.

The gas composition of the air is determined either by binding oxygen and carbon dioxide chemically in a Haldane gas-analysis apparatus, or by the physical methods more recently employed, using

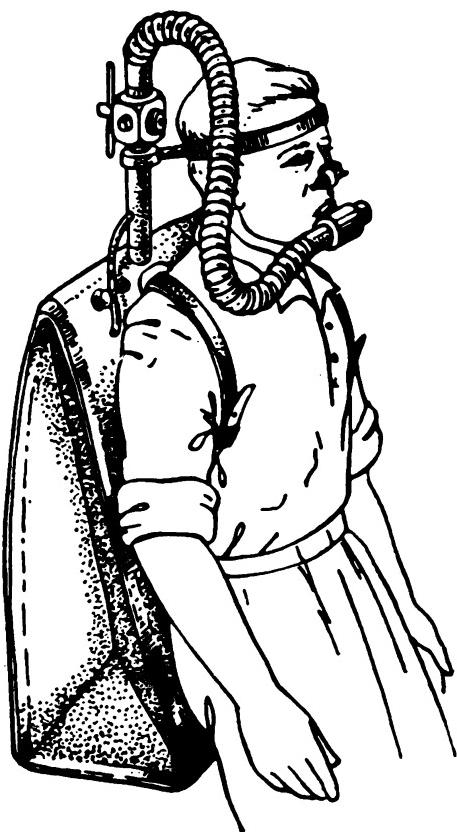


**FIG. 94. Diagram of the respiratory apparatus devised by M. N. Shaternikov**  
**Ch.** — chamber; **Cyl.** — oxygen cylinder; **M** — motor for pumping air out of the chamber; **P** — coil pipe for cooling the air; **A** — vessel filled with an alkaline solution that absorbs carbon dioxide; **W** — cylinder filled with calcium chloride that absorbs water vapours; **T** — thermometers. A device for automatical supply of oxygen into the chamber and maintenance of a constant pressure in it is shown on the left

electronic instruments (these methods are based on certain physical features of the gases: viz. the paramagnetic properties of oxygen, the heat conductivity of carbon dioxide, etc.).

When the chemical method is used, the volume of air collected for analysis is first measured and then passed through a solution containing an alkali that absorbs carbon dioxide, the volume of the air is somewhat reduced as a result, and the percentage of carbon dioxide in it is calculated from the difference between the volumes before and after absorption. The oxygen content is then determined in a similar manner by passing the remaining air through a solution of pyrogallol, which absorbs oxygen. Since the experiments may be conducted at different temperatures and pressures, the volumes of the two gases are recalculated to their volumes at 0°C and 760 millimetres pressure to obtain comparable results. The results of analysis of the samples are used to calculate the amounts of oxygen and carbon dioxide in the entire volume of expired air.

The oxygen absorbed by the organism is used to oxidize proteins, fats, and carbohydrates. The amounts of oxygen needed to oxidize one gramme of each of those substances, and the amount of heat liberated during the process, differ with the substance. It may be seen from the table that the oxidation of one gramme



**FIG. 95.** Estimation of pulmonary ventilation using a Douglas bag. The horizontal tube connected with the mouth-piece has valves which allow to inhale the atmospheric air and to exhale it into the bag. A clip is applied to the nose to obstruct nasal respiration

of carbohydrate liberates 4.1 kilocalories in the body, the process requiring 0.830 litre of oxygen. Therefore, if one litre of oxygen is consumed and used to oxidize carbohydrates, 5.05 kilocalories will be released. The oxidation of one gramme of protein also releases 4.1 kilocalories, but the amount of oxygen used up is greater, namely 0.970 litre. Consequently, with one litre of oxygen utilized to oxidize protein, 4.46 kilocalories will be released in the organism. When one litre of oxygen is expended in oxidizing fats, 4.74 kilocalories are released.

Substance oxidized in the body	Oxidation of 1 g of nutrients		Heat released on consumption of 1 litre of O <sub>2</sub> , Cal
	heat released, Cal	O <sub>2</sub> utilized, litres	
Proteins	4.1	0.970	4.46
Fats	9.3	2.030	4.74
Carbohydrates	4.1	0.830	5.05

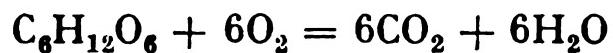
The amount of heat generated by the utilization of one litre of oxygen in the organism is known as *calorific value of oxygen*. As will be seen from the figures given above, its value varies with the substance oxidized.

Thus, with the amount of consumed oxygen measured, energy expenditure can be calculated only if it is known what substances

(protein, fat, or carbohydrate) were oxidized. In experimental studies of the gas exchange that can be indicated by the respiratory quotient.

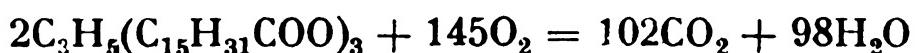
#### THE RESPIRATORY QUOTIENT AND ITS SIGNIFICANCE IN STUDIES OF METABOLISM

The *respiratory quotient* is the ratio between the volume of carbon dioxide released and the volume of oxygen consumed. It varies according to whether proteins, fats, or carbohydrates are oxidized. Let us first consider its value for the carbohydrates utilized by the organism, taking glucose as an example. The total result of the oxidation of a molecule of glucose can be expressed by the following formula:



The equation of the reaction shows that the number of carbon dioxide molecules produced by the oxidation of glucose is equal to the number of oxygen molecules consumed (absorbed). An equal number of gas molecules occurring at the same temperature and pressure occupy equal volumes (Avogadro's law). Therefore, the respiratory quotient (the  $\frac{\text{CO}_2}{\text{O}_2}$  ratio) here is 1.0. The quotient has the same value for the oxidation of other carbohydrates.

When fats and proteins are oxidized the respiratory quotient is less than 1.0, and is 0.7 for fats. That can be shown from the results of oxidizing any fat. Let us take tripalmitin as an example:



The volumetric relation of carbon dioxide and oxygen in that case is:

$$\frac{102\text{CO}_2}{145\text{O}_2} = 0.703$$

Similar calculations may be made for proteins; when they are oxidized in the organism the respiratory quotient is 0.8.

With a mixed diet the respiratory quotient in man varies as a rule between 0.85 and 0.9.

Since the number of kilocalories liberated by the utilization of one litre of oxygen varies with the nutrient oxidized, it must also differ with the value of the respiratory quotient for the substances oxidized in the organism. Each definite respiratory quotient has a corresponding calorific equivalent of oxygen as may be seen from the following table:

Respiratory Quotient	0.70	0.75	0.80	0.85	0.90	0.95	1.0
Calorific value of oxygen	4.686	4.739	4.801	4.862	4.924	4.985	5.047

In certain circumstances, at the end of strenuous muscular work for example, the value of the respiratory quotient calculated over a short interval does not reflect the consumption of proteins, fats and carbohydrates.

#### THE RESPIRATORY QUOTIENT DURING WORK

With strenuous muscular effort the respiratory quotient rises and comes close to 1.0 in most cases, because the main source of energy then is carbohydrate oxidation. In the first few minutes after the work has ended, known as the period of recovery, it rises sharply and may even exceed 1.0. Then it falls sharply below its initial levels and may only return to normal values, for example, 30 to 50 minutes after the end of two hours of strenuous effort. These changes in the respiratory quotient are shown in Fig. 96. The alterations in the quotient encountered at the end of work do not reflect the true relationship between the oxygen consumed at that moment and the

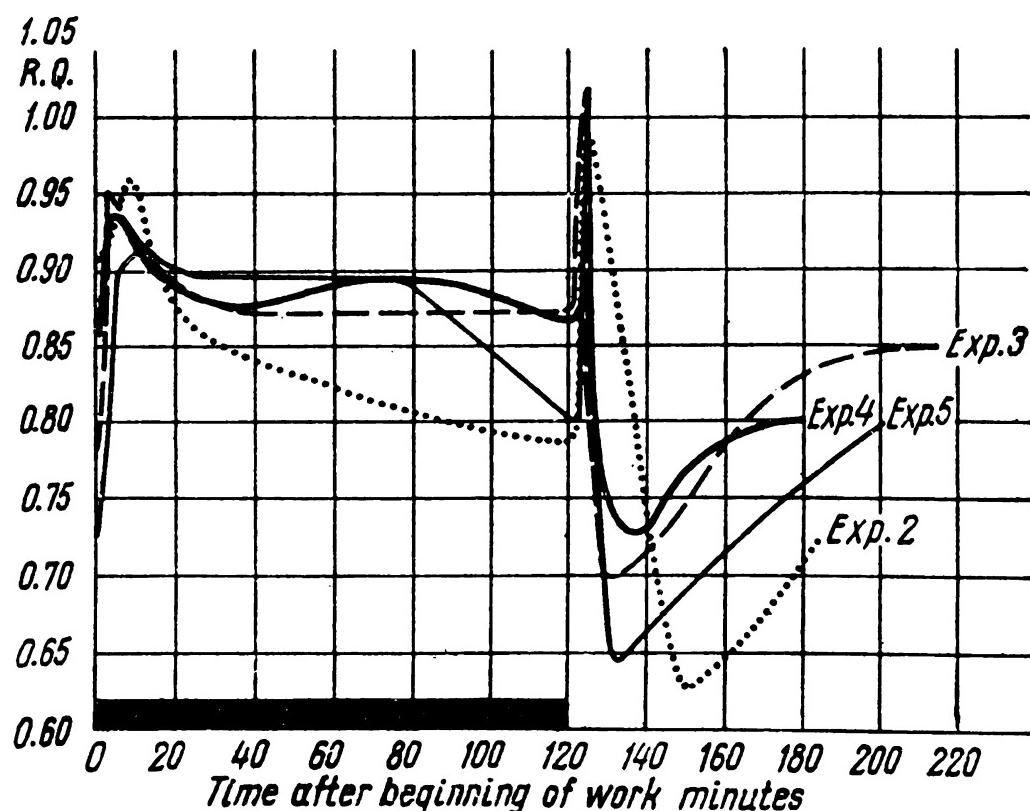


FIG. 96. Respiratory quotient curves during and after two hours of strenuous work, observed in four cases (after Talbot, Henderson, Dill, et al.)

carbon dioxide given off. The reason for its rise at the beginning of the period of recovery is as follows: lactic acid accumulates in the working muscles and there is not sufficient oxygen to oxidize it during the period of effort (oxygen debt, p.210). The lactic acid escapes into the blood and displaces carbon dioxide from the bicarbonates, combining with the bases. In consequence the volume of carbon dioxide eliminated is greater than that formed in the tissues at the given moment. A reverse picture is encountered in the next period as the lactic acid gradually disappears from the blood. Some of it is oxidized, some is resynthesized into the initial product, and the rest is discharged in urine and sweat. As its amount decreases, the bases that were taken away from bicarbonates are released, and re-form bicarbonates, which is why the respiratory quotient falls sharply some time after muscular exercise owing to the retention in the blood of the carbonic acid given off by the tissues.

#### BASAL METABOLISM

The magnitude of energy transformation and total metabolism depends a) upon the individual features and condition of the organism (sex, age, weight and height, the conditions and character of its nutrition, muscular work, the state of the endocrine glands, nervous system, and internal organs like the liver, kidneys, and alimentary tract, and so on) and b) upon the conditions of the external environment (temperature, barometric pressure, the humidity and composition of the air, the effect of radiant energy, etc.).

The minimum level of metabolism and energy expenditure encountered in a wide-awake organism under definite conditions is known as its *basal metabolism*.

To determine an individual's basal metabolism he has to be examined: 1) in a state of muscular rest (lying down with his muscles completely relaxed), and isolated from stimuli that excite emotion; 2) while fasting, i. e. 12 to 16 hours after a meal; 3) at a "comfortable" temperature of 18° to 20°C, i. e. at a temperature that neither causes a feeling of cold or shivering nor produces overheating of the body.

Most of the basal metabolic energy is utilized for the work of the respiratory muscles, heart, kidneys, and liver. The constancy of the body temperature is maintained by the energy expenditure arising from basal metabolism.

**Normal values of basal metabolism in man.** The basal metabolic rate (BMR) is usually expressed by the amount of heat in kilocalories per kilogram of body weight or per square metre of body surface per hour or 24 hours.

The basal metabolic rate of a human of average age (about 35), average height (about 165 centimetres), and average weight (about

70 kilograms) is one kilocalorie per kilogram per hour. The BMR of an adult male weighing 70 kilograms averages 1,700 kilocalories per 24 hours, while that of an adult female of the same weight is approximately 10 per cent lower.

The basal metabolic rate of children, calculated per kilogram of body weight, is considerably higher than that of adults. BMR in man stays at a fairly constant level between the ages of 20 and 40 if no sharp changes in the state of the organism occur (with no marked changes in body weight and no illnesses). Thus Zuntz measured his own basal metabolism periodically for a period of 22 years and found that the results gave deviations of no more than  $\pm$  7 per cent from the mean value. The basal metabolic rate decreases with advanced age.

If the individual's body weight, height, and age, or the surface area, are known, his basal metabolic rate can be calculated by means of special formulae and tables. According to Dreyer's formula, the BMR for 24-hours expressed in kilocalories ( $H$ ) is:

$$H = \frac{\sqrt{W}}{K \times A \cdot 0.1333}$$

where  $W$  is the body weight in grammes,  $A$  is the age of the individual, and  $K$  is a constant (0.1015 for males and 0.1129 for females).

The formulae and tables are compiled from statistical data, i. e. they give the mean values of a great number of basal metabolic rates yielded by studies of individuals of both sexes and different ages, with different body weights and heights.

Estimates of the basal metabolic rate of healthy individuals with a normal body build made from these tables give approximately correct values of energy expenditure (error of  $\approx$  5 to 8 per cent). Rates that are disproportionately high for the given weight, height, and age are encountered in hyperactivity of the thyroid gland and in certain other illnesses. Reduced rates are observed with deficient activity of the thyroid (myxoedema), pituitary, and sex glands.

During sleep the rate of energy exchange decreases by 8 to 10 per cent compared with the values observed in the waking state because the muscles of a sleeping individual are in a state of maximum relaxation. Elevation of body temperature has an extremely marked effect on energy exchange; with a one degree rise in the body temperature in man energy expenditure increases by an average of 10 to 11 per cent.

Climate also influences the rate of metabolism. Thus the BMR of individuals living in the tropics is 90 to 80 per cent that of subjects at middle latitudes, while the rate of persons living in the north is higher in the cold months.

## SURFACE LAW

Calculations of basal metabolic rate per kilogram of weight show that in warm-blooded animals it varies greatly with the species, and in man with weight and height; but the values for various animals and humans show less discrepancy when one square metre of body surface is used as the standard of reference.

Object of examination	Body weight, kg	Heat production per 24 hours, kilocalories	
		per kg of body weight	per m <sup>2</sup> of surface area
Mouse	0.018	654.0	1,188
Fowl	2.0	71.0	947
Goose	3.5	66.7	967
Dog	15.2	51.5	1,039
Man	64.3	32.1	1,042
Pig	128.0	19.1	1,078
Bull	391.0	19.1	1,567

From data pointing to the existence of a regular relationship between the basal metabolic rate and body surface area Rubner and others have advanced a *surface law*, according to which, the energy expenditure of warm-blooded animals is proportional to their surface area.

The daily heat production per square metre of body surface in man is 850 to 1,250 kilocalories, the average for a male being 948 kilocalories.

Surface area ( $R$ ) is estimated from the formula

$$R = K \times \text{weight}^{2/3}$$

which is based on analysis of results obtained by direct measurement of the body surface. The constant  $K$  for man is 12.3.

A more exact formula has been suggested by Dubois:

$$R = W^{0.425} \times H^{0.725} \times 71.84$$

where  $W$  is the body weight in kilograms and  $H$  is the height in centimetres. The result is expressed in square centimetres.

The surface law is not absolutely correct, and as may be seen from the table given above it is only a rule; but it has definite practical significance for approximate estimates of the amount of energy released by the organism.

That this law is not absolute is shown by the fact that basic metabolic rate may differ widely in two individuals of identical surface area. The level of oxidation processes is determined not so

much by the heat emission of the body surface as by the heat emission of the cells, which is governed by the activity of the nervous system and the condition of the endocrine apparatus.

#### EXCHANGE OF ENERGY DURING PHYSICAL WORK

Muscular activity increases energy expenditure considerably, which is why the daily expenditure of a healthy individual who spends part of the day moving about and performing physical work is very much greater than his basal metabolic rate. The increase in energy expenditure is the "work allowance", which varies with the intensity of the muscular exertion.

With muscular work thermal and mechanical energy are released. The ratio of the mechanical energy to the total utilized for work, expressed as a percentage, is known as the *mechanical efficiency* of the organism. It varies between 16 and 25 per cent in man during work, and averages 20 per cent, but in some cases it may be higher.

Mechanical efficiency varies according to a number of conditions; it is lower in untrained individuals and rises with training.

The amount of energy expended is in direct proportion to the intensity of the muscular work performed, which can be seen from the following data: energy expenditure in basal metabolism averages one kilocalorie per kilogram per hour; in an individual sitting quietly it averages 1.4 kilocalories per kilogram per hour, and in an individual standing relaxed 1.5 kilocalories; light work requires 1.8 to 2.5 kilocalories; the light muscular work involved in walking requires 2.8 to 3.2 kilocalories; occupations that involve moderate muscular exertion require 3.2 to 4 kilocalories; while heavy physical labour requires 5.0 to 7.5 kilocalories.

The various occupations can be divided into a number of groups according to daily energy expenditure as follows.

Group I	Individuals engaged in mental work (scientists, doctors, engineers, office workers, etc.)	3,000 to 3,200 kilocalories
Group II	Operators of machines (turners, milling machine operators, textile workers, public transport drivers, etc.)	3,500 kilocalories
Group III	Workers engaged in partially mechanized physical work (fitters and toolmakers, stokers, agricultural workers)	4,000 kilocalories
Group IV	Workers engaged in heavy physical work (dockers and porters, navvies, etc.)	4,500 to 5,000 kilocalories

The energy expenditure of workers is significantly reduced with the introduction of machinery in agriculture, building, and industry.

## **EXCHANGE OF ENERGY DURING MENTAL WORK**

Energy expenditure is considerably less in mental work than in physical effort.

Difficult calculations, work on a book, and other types of mental work not accompanied by movement cause an insignificant (2 to 3 per cent) increase in the amount of energy expended compared with complete rest. But in most cases mental work involves muscular activity, especially if the individual is excited emotionally (lecturers, actors, writers, speakers, etc.), and energy expenditure may be relatively high. Emotional excitation can raise the metabolic rate by 11 to 19 per cent, over a period of days.

Metabolism will double or more in most subjects convinced by suggestion that they are doing heavy muscular work. These facts indicate that the metabolism and energy expenditure of the organism may alter under the influence of the cortex of the cerebral hemispheres.

## **THE SPECIFIC DYNAMIC ACTION OF FOODS**

Intake of food and the assimilation of nutrients by the cells increase the energy expenditure of the organism and intensify metabolism, causing an increase in metabolism and energy exchange known as the *specific dynamic action of foods*.

Protein foods possess the highest specific dynamic action, raising the metabolic rate by 30 per cent on average. With carbohydrates and fats it is less marked. A diet of fats and carbohydrates raises metabolism in man by 4 to 15 per cent (reports by different researchers vary).

## **NUTRITION**

The object of physiologists in substantiating rational nutrition is to indicate the composition and amounts of foods that will meet the organism's requirements. The concepts food and foodstuff should not be confused with that of nutrient. The last term embraces definite groups of chemical compounds: viz. proteins, fats, carbohydrates, mineral salts, vitamins, and water, which are contained in one amount or another in foodstuffs, most foods being mixtures of a number of them.

## **HEAT OF COMBUSTION VALUES OF NUTRIENTS**

The energy value of the food eaten can be estimated if its composition and assimilability have been determined, since the heat of combustion values of nutrients are known.

The heat of combustion value of a nutrient is the quantity of heat produced on combustion of one gramme of it. According to Rubner, the value for the main nutrients is as follows:

1 gramme of protein	4.1 kilocalories
1 gramme of fat	9.3 kilocalories
1 gramme of carbohydrate	4.1 kilocalories

These values are determined by means of a Berthelot *bomb calorimeter*, a sealed vessel immersed in water in which the substance being studied is burned under high oxygen pressure; the amount of heat produced is determined by the rise in temperature of the known volume of water surrounding the bomb.

The results obtained by determining the heats of combustion of fats and carbohydrates in a bomb calorimeter are identical with those yielded by studies of the amount of energy produced in the organism when they are oxidized, which accords with the law enunciated by Hess in 1840 that the thermal effect of chemical reactions is the same if their initial and final products are the same, independent of the intermediary stages. Fats and carbohydrates whether oxidized in the organism or burned outside it yield the same end products, carbon dioxide and water; the amounts of heat produced in both cases, therefore, must be equal. Unlike fats and carbohydrates, proteins produce more heat when burned in a calorimeter than when they are oxidized in the organism. Thus, 5.85 kilocalories are produced when one gramme of casein is burned, but only 4.1 kilocalories when it is oxidized in the organism. That is explained by the fact that proteins are reduced to  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and  $\text{NH}_3$  in the bomb, while their oxidation in the body yields end products (urea, uric acid, and creatinine) which themselves possess a fairly high heat-producing capacity.

Gross and net heat of combustion values are distinguished. The former is the total calorific value of the food consumed, while the latter allows for assimilability; thus the net calorific value expresses the number of kilocalories actually received by the organism from a given food.

#### ASSIMILABILITY OF FOODS

Not all the food eaten is assimilated, i. e. absorbed from the alimentary tract and utilized in the organism; some is eliminated from the intestine as waste. The assimilability of a food is determined by subtracting the amount of protein, fat, and carbohydrate in the faeces from the amount in the food itself.

Assimilability averages 95 per cent with animal food, 80 per cent with vegetable food, and 82 to 90 per cent with a mixed diet.

In practice 90 per cent is usually adopted as the standard for calculations.

#### ISODYNAMIC LAW

The amount of energy required by the organism can be supplied by the oxidation of proteins, fats, or carbohydrates. Taking only its energetics into account, Rubner formulated an *isodynamic law* that the different nutrients can replace one another in accordance with their heat of combustion values. According to this law, one gramme of fat, which yields 9.3 kilocalories in the organism, can be replaced by 2.3 grammes of carbohydrate or protein, while one gramme of protein, which generates 4.1 kilocalories can be replaced by one gramme of carbohydrate or 0.44 gramme of fat. Rubner himself, however, pointed out that the significance of his isodynamic rule is extremely limited since it only takes into account the energy requirements of the organism, while the substances contained in food (proteins, lipoids) actually perform other functions as well, serving as building material for the constituents of cell protoplasm that are continuously destroyed in the process of metabolism. Therefore recommendations of dietary allowances should not be governed solely by the isodynamic law, which applies only to the calorific value of the food. The body must also receive adequate amounts of proteins, fats, carbohydrates, salts, and vitamins.

#### DIETARY STANDARDS FOR MAN

The problem of protein allowances in nutrition is most important in theory and practice in preparing recommendations of dietary rations.

Research into the amounts of protein required by man began in the sixties of the last century. At that time one of the founders of the physiology of nutrition, C. Voit, concluded, from determination of the amount of nitrogen excreted by man, and from statistical data on the average composition and intake of foods, that the daily protein requirement of an adult engaged in moderate physical work was 118 grammes.

Certain researchers in the West, particularly in the USA, have repeatedly studied how far protein intake can be reduced without causing a shift in nitrogen equilibrium toward a negative balance, i. e. without producing a state of protein starvation. These authors have tried to determine the *protein minimum*, i. e. that least amount of proteins with which nitrogen equilibrium can still be maintained.

For that purpose Chittenden conducted experiments on 26 individuals, himself included, for an average period of eight months. The daily protein intake in his experiments averaged between 50 and 60 grammes. It was found that the nitrogen equilibrium was established in some of the subjects but not in others, and that

those subjects showed a significant loss of weight (as much as six kilograms within eight months) and became exhausted.

Hindhede concluded, also from long-term experiments employing potatoes (which are rich in carbohydrates and poor in proteins) as the main food, that that protein allowance in the diet could be further reduced. He considered a daily protein intake of 25 to 35 grammes sufficient although he himself and all the subjects studied by him had a chronic negative nitrogen balance. Thus, his results justified a conclusion diametrically opposite to his own point of view, namely, that a sharp reduction in the daily protein allowance in the diet is inadmissible.

The unfavourable effect of prolonged protein deficiency shows itself only after a fairly long interval of time. It has been demonstrated in particular that resistance to infection is reduced with a poor protein intake. The protein content of the diet should exceed the minimal body requirements for nitrogenous compounds since a definite reserve of protein is needed that can be mobilized when the physiological activity is intensified, considerations which have led Soviet scientists (Shaternikov, Lavrov, Zbarsky, and others) to conclude that a sharp restriction of the protein intake is undesirable.

Recommendations on dietary allowances should not be guided by the protein minimum, but by the *protein optimum*, that is, by that amount of protein in the diet that will meet the requirements of the organism, ensure well-being, high working capacity, adequate resistance to infection, and in children satisfy their growth needs. The daily allowance of protein that will satisfy the requirements of a human adult engaged in light work under normal physiological conditions average between 80 and 100 grammes.

Individuals engaged in moderate physical work require between 150 and 160 grammes, and not less than 30 per cent of it of animal origin.

For children, protein allowances per kilogram of body weight should be increased owing to the needs of growth. Molchanova has given the following daily protein requirements for children: between one and three years 55 grammes, between four and six 72 grammes, between seven and nine 89 grammes, and between ten and fifteen 100 to 106 grammes.

The diet should include a minimum of 60 grammes of fats since they contain fat-soluble vitamins and lipoids essential for the building of cells. With a daily expenditure of 3,000 kilocalories, 100 grammes of fats are recommended, and fats of animal origin should account for 30 to 50 per cent of that amount.

The diet must also contain carbohydrates, mineral salts, and an adequate quantity of vitamins. The carbohydrate content of the daily diet should be between 400 and 500 grammes.

## TEMPERATURE REGULATION

### BODY TEMPERATURE AND HOMOIOOTHERMY

The body temperature of humans and higher animals is maintained at a relatively constant level despite variations in the temperature of the external environment. This constancy of body temperature is known as *homoiothermy*.

It is characteristic only of *homoiothermic* or warm-blooded animals and is not encountered in *poikilothermic* or cold-blooded animals, in which body temperature varies and differs little from the temperature of the external surroundings.

Homoiothermy develops gradually in the course of ontogenesis. In the newborn infant the ability to maintain a constant body temperature is far from perfect, so that cooling of the body (*hypothermia*) or overheating (*hyperthermia*) can occur at external temperatures that have no effect on an adult. Equally, even slight muscular exercise, like that of a baby crying for a long time, can raise body temperature. The organism of a premature infant is even less capable of maintaining a constant body temperature, and is markedly influenced by the surrounding temperature.

The temperature of the organs and tissues, and equally, the temperature of the organism as a whole, depends upon the rate of heat production and heat loss.

*Heat production* arises from continuously occurring exothermal reactions, which occur with varying intensity in all organs and tissues and are attended with the liberation of heat. More heat is produced in actively working tissues and organs (the muscles, liver, and kidneys) than in less active ones (connective tissue, bones, and cartilage).

The heat loss suffered by organs and tissues greatly depends on where they are located; organs that lie close to the surface, like the skin and skeletal muscles, give off more heat and cool more easily than internal organs which are better protected.

It is clear therefore that the various organs must have different temperatures. The liver, which lies deep in the body and gives off heat in large amounts, has the highest temperature in man ( $37.8^{\circ}$  to  $38^{\circ}\text{C}$ ), while the temperature of the skin is much lower ( $29.5^{\circ}$  to  $33.9^{\circ}\text{ C}$  on areas covered by clothes).

From that it follows that the concept of body temperature is conditional since temperature differs so much in the various parts of the body. The mean temperature of the body as a whole is best characterized by the temperature of the blood in the main vessels, since the blood flowing along them is heated in the active tissues, cooling the latter at the same time, and is cooled in the skin thus warming it in turn.

The body temperature of humans is commonly estimated by measuring it in the axilla, where it is  $36.5^{\circ}$  to  $36.9^{\circ}\text{C}$  in a healthy

individual. In clinical practice, particularly in paediatrics, rectal temperature is often measured; it is higher than the axillary and averages between 37.2° and 37.5°C in a healthy subject.

Body temperature does not remain constant, but varies during the day within 0.5° to 0.7° C being highest between 16:00 and 18:00 hours and lowest between 3:00 and 4:00. The variations depend upon the way of life; rest and sleep cause a fall in temperature, while muscular effort is attended by a rise. The diurnal variations in individuals who work at night for long periods may therefore be the opposite of those mentioned above.

Constancy of body temperature can only be maintained if the heat production of the organism is balanced by its heat loss, which is achieved by physiological mechanisms of temperature control. It is customary to divide this thermoregulation into physical and chemical.

*Chemical thermoregulation* is effected by increasing or reducing heat production in the organism, i. e. by increasing or reducing the intensity of metabolism. *Physical thermoregulation* is effected by altering the rate of heat loss.

#### CHEMICAL THERMOREGULATION

One of the factors determining the intensity of metabolism and consequently the rate of heat production, is the temperature of the surroundings.

With a rise in the temperature of the environment to 25° or 30°C, metabolism and heat production fall a little. On the other hand, a drop in the surrounding temperature below 15°C causes a marked increase in heat production. Generation of heat is significantly increased if the temperature of the surroundings drops below the optimal level, or *comfort zone*. For an individual wearing normal light clothing that zone varies between 18°C and 20°C, for a nude subject it is 28°C.

The optimum temperature for an individual rises when he is immersed in water because of its high heat capacity and heat conduction; its cooling effect on the body is fourteen times that of air, so that the metabolic rate of an individual lying in a cool bath rises greatly compared with his rate at the same air temperature.

An increase of heat production with a fall in environmental temperature is most important for control of body cooling.

The most active heat production occurs in the muscles during contraction. When an individual is lying still but has his muscles tensed, oxidation processes, and with them heat production, increase by 10 per cent and more compared with their values when he is lying with his muscles completely relaxed. A relatively small motor activity leads to a 25 per cent increase in heat generation. Walking

causes a rise in energy expenditure of 60 to 80 per cent, and heavy physical labour by as much as 400 or 500 per cent.

Heat production in the muscles is increased in cold conditions since the cooling of the body surface acts upon the cold receptors of the skin and causes sporadic, involuntary reflex contractions of the muscles expressed as shivering. With it the energy expenditure of the organism rises sharply, and the consumption of oxygen and carbohydrates by the muscular tissues is raised, leading to intensification of heat production. Thus a chill, or shivering in the cold, is a manifestation of reflex control of body temperature effected by heightened heat production in the muscles. How much shivering can raise heat production can be seen from the fact that artificial simulation of shivering increases it by 200 per cent from the initial level. The importance of shivering is also shown by the fact that body temperature drops much faster through cooling if a subject is administered muscle relaxants, substances that interfere with the conduction of impulses from the nerves to the muscles and so suppress reflex muscular shivering.

Apart from the muscles, the liver and kidneys play an important role in chemical thermoregulation. The temperature of the blood in the hepatic vein is higher than that in the hepatic artery, which points to active heat production in the liver; the process is intensified when the body is cooled.

Energy is liberated in the body as the result of the oxidative breakdown of proteins, carbohydrates, and fats, so that it is clear that all mechanisms regulating oxidation processes are also involved in the regulation of heat production.

#### PHYSICAL THERMOREGULATION

Physical thermoregulation is exceptionally important in maintaining a constant body temperature when the temperature of the environment rises. The metabolic rate falls when the surrounding temperature comes close to or equals that of the body, but that cannot of itself prevent overheating of the organism since much heat is still generated in it. A state of homiothermy is then maintained mainly by physical thermoregulation through intensification of heat loss. The heat produced in the organism is lost mainly by *heat emission (radiation)* and by *convection*, i. e. by being given off by the skin directly into the air or to the objects immediately in contact with its surface. Heat emission and convection together account for about 70 per cent of the total heat loss of an adult (radiation for 55 per cent and convection for about 15 per cent).

Under normal conditions, and with no active work being done, about 27 per cent of the heat is eliminated by the evaporation of water from the surface of the skin and lungs. Considering that the sweat glands eliminate about 500 millilitres of water in 24 hours

and the lungs about 350 millilitres, and that the evaporation of one millilitre of water requires 0.58 kilocalorie, it is clear that some 500 kilocalories are expended on evaporating water from the body. The heating of expired air and excreted faeces accounts for 3 per cent of the body's heat loss.

Clothing reduces heat loss because the layer of still air between it and the skin, being a poor conductor of heat, hinders its escape. The temperature of the air under clothes may be as high as 30°C. On the contrary, a nude body loses heat because the air on its surface is continuously being replaced. Hence the temperature of exposed skin surfaces is much lower than that of the clothed parts.

Heat loss is greatly prevented by subcutaneous adipose tissue owing to the low heat conduction of fat.

Heat emission and convection can be studied together as they parallel one another and are governed by the same factor, i. e. the temperature difference between the skin and the surroundings. Skin temperature, and consequently radiation and convection, may alter a) through redistribution of the blood in the blood vessels, and b) through a change in the volume of blood flow.

Redistribution of the blood in the various vascular regions occurs in the following manner: the skin vessels, the arterioles in particular, become constricted in the cold and great amounts of blood escape into the vessels that supply the abdominal organs. The surface layers of the skin, receiving less warm blood, radiate smaller amounts of heat and thus warm the surroundings less and heat convection decreases. With severe cooling of the skin of the extremities the arteriovenous anastomoses open as well, so that the volume of blood flowing into the skin capillaries is reduced and loss of heat hampered.

With a high external temperature, the skin vessels become dilated and warm blood flows to the skin, raising its temperature, and so increasing radiation and heat convection.

This increase in the volume of circulating blood is due to the passage of water from the tissues into the blood and to the release of an additional amount of blood from the spleen and other blood reservoirs. Reverse phenomena are responsible for the marked decrease in the amount of circulating blood in the cold. It is evident that an increase in the volume of the circulating blood augments blood flow in the skin, which raises the transfer of heat from its surface to the surroundings.

The evaporation of sweat from the skin plays an essential role in maintaining body temperature constant when the temperature of the surroundings is high, and the body loses large quantities of heat in that way.

The significance of sweating is clearly shown by the following calculation. In the tropics the temperature frequently reaches 37°C, i. e. matches the temperature of the human body. That means

that the organism of a man living under such conditions cannot give off its own heat by radiation and convection. The only mode of heat loss is by evaporation. Accepting that 2,400 to 2,800 kilocalories is the average value of daily heat production, and knowing that the evaporation of one gramme of water from the body surface requires 0.58 kilocalorie, we find that 4.5 litres of water must be evaporated to maintain body temperature constant under such conditions. The elimination of sweat is considerably intensified but production of heat in the organism itself increases when muscular work is done in hot surroundings. The amount of sweat given off daily by men engaged in very hard work in hot shops may be as high as 12 litres.

Evaporation depends upon the relative humidity of the air and cannot occur in air saturated with water vapour, which is why a high temperature is more distressing with high humidity. In an atmosphere saturated with water vapour, in a Turkish bath, for example, profuse perspiration occurs; the sweat, however, does not evaporate but runs down the body. That type of perspiration does not contribute to heat loss, only the sweat that evaporates from the skin is important for heat loss (this sweat comprises the "effective perspiration").

Clothing impermeable to air (leather or rubber) causes distress because the layer of air between the clothes and the body soon becomes saturated with vapours and the evaporation of sweat ceases.

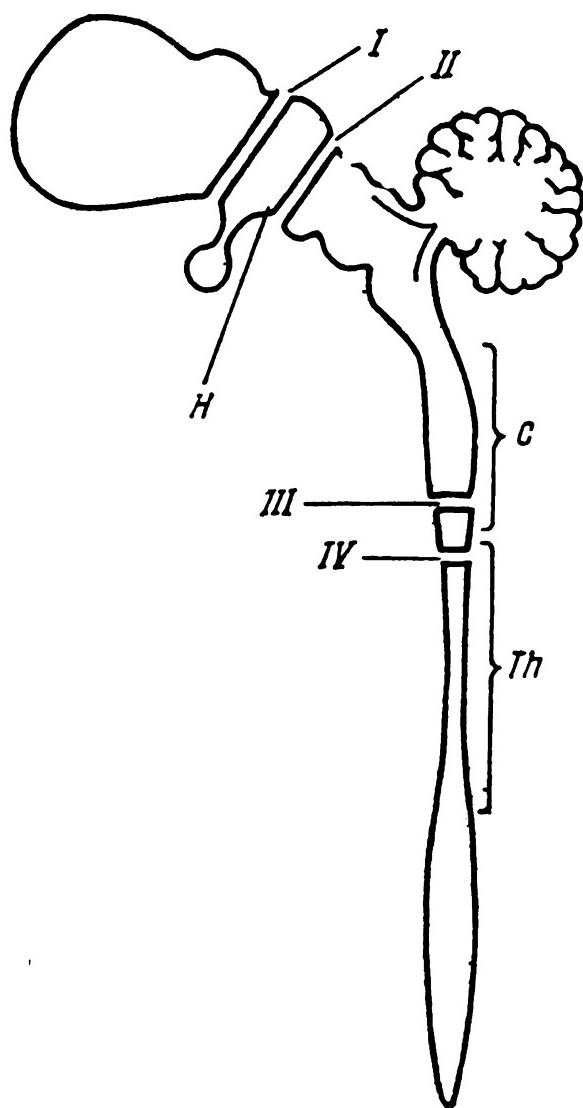
The importance of evaporation is also evident from the fact that even a relatively moderate temperature ( $32^{\circ}\text{C}$ ) is endured with difficulty if the air is humid. But if the air is completely dry an individual can remain in a temperature of  $50^{\circ}$  to  $55^{\circ}\text{C}$  for two or three hours without signs of overheating.

Some water is vaporized in the lungs and saturates the expired air. In that way respiration also contributes to the maintenance of a constant body temperature. Cold causes reflex inhibition of the respiratory centre and the rate of breathing falls; with a high environmental temperature, on the contrary, the centre is stimulated.

It follows from the foregoing that the body temperature is governed by the combined effect of the mechanisms that control the rate of metabolism and the heat production dependant on it (chemical heat regulation), and those that control blood supply to the skin, perspiration, and respiration (physical heat regulation).

#### THE NERVOUS MECHANISM OF THERMOREGULATION

The importance of the central nervous system in thermoregulation was established long ago in the experiment known as *heat puncture*. Injury inflicted on definite parts of the diencephalon with a long



**FIG. 97. Diagram illustrating the nervous mechanism of thermoregulation (after Best and Taylor)**

*H* — hypothalamus; *C* — cervical portion of spinal cord; *Th.* — thoracic portion of spinal cord; *I* — dissection of the brain stem, that does not interfere with normal thermoregulation; *II* — dissection of the brain stem, that causes sharp impairment of thermoregulation; *III* — dissection of the spinal cord, that causes complete loss of thermoregulation; *IV* — dissection of the spinal cord, that causes loss of physical thermoregulation but does not interfere with chemical regulation

thin needle caused a marked rise in the body temperature of a rabbit by  $2.5^{\circ}\text{C}$  to  $3^{\circ}\text{C}$ . The role of the various parts of the central nervous system in control of heat production and loss has also been studied by cutting the spinal cord at various levels (Fig. 97).

Those experiments revealed the localization of the *heat-regulating centres*, that is, of a group of nerve cells concerned with co-ordinating the numerous complex vegetative processes responsible for maintaining body temperature constant.

Other experiments have shown that removal of the cerebral cortex, the corpus striatum, or the optic thalamus has no marked effect on the processes of heat loss or heat production. But with resection of the hypothalamus an animal loses its ability to regulate the temperature of its body and becomes poikilothermic.

Renson and his co-workers studied the localization of the centres in the hypothalamus; by damaging its various parts he revealed the presence of nuclei that regulate the processes of heat production and of others that control heat loss. The *centre of heat production* (or *thermogenic centre*) lies in the caudal portion of the lateral hypothalamic nuclei. Animals in which this part of the brain has

been destroyed cannot endure cold, their mechanisms of chemical thermoregulation do not function and shivering, in particular, does not occur in response to cold. Physical thermoregulation (perspiration, acceleration of respiration) is controlled by that part of the hypothalamus lying between the commissura anterior and the chiasma opticum. Destruction of that region — the *centre of heat loss* or the *thermolytic centre* — does not interfere with the animal's ability to endure cold, but overheating easily occurs at high temperatures in the surroundings because the mechanism responsible for physical thermoregulation has been damaged.

Although removal of the cerebral hemispheres has no marked effect on either of the processes, it would be unjustified to conclude that these structures and their cortex have no influence on heat exchange. Experiments on animals and observations of human subjects have shown that the dissipation and generation of heat can be altered by conditioned reflexes which, like all conditioned reflexes, are effected by the cerebral cortex.

The main stimulators of the heat-regulating centres are nerve impulses conducted to the central nervous system from the heat and cold receptors in the skin and mucous membranes. Through these impulses the temperature of a body exposed to heat or cold is controlled reflexly. The direct action of cooled or warmed blood on the heat-regulating centres also has a certain significance, as was shown by an experiment in which shivering of the muscles of the head and upper part of the trunk occurred in an animal when his hind limbs, which had lost sensation through severing of its thoracic spinal segments, were put into cold water. The cooling of the limbs lowered blood temperature and that stimulated the centres of heat production. Evidence of the direct influence of cold or heat on the thermoregulation centres has been obtained from experiments in implanting a special tube into the brain of dogs so that it touched the subcortical nuclei. Heat production increased when cold water was passed through the tube, while the body temperature fell when warm water was introduced. Similar results can be produced by heating or cooling the carotid artery supplying the brain.

Dissection of the brain below the level of the heat-regulating centres deprives the organism of its ability to intensify oxidation processes in response to cooling. A similar effect is caused by injuries to the pathways from the centre of chemical thermoregulation to the periphery, maintenance of constant body temperature in surroundings with a falling temperature therefore becomes virtually impossible after dissection of the cervical portion of the spinal cord. The procedure also suppresses physical thermoregulation through sweating and changes in the diameter of the skin vessels, which is explained by the fact that the nerve fibres responsible for vasoconstriction and sweating originate in the thoracic and lumbar segments of the spinal cord.

## HUMORAL MECHANISM OF THERMOREGULATION

The endocrine glands also participate in the regulation of body temperature, especially the thyroid and adrenals, whose hormone-forming activity is controlled by the nervous system.

The participation of the thyroid gland is shown, for instance, by an experiment in which the metabolic rate in an animal is increased by injecting blood serum from another animal which has been kept in the cold for a long time. (The effect is only encountered, of course, if the thyroid of the donor animal has not been removed.) Release of metabolism-activating thyroid hormone into the blood is apparently accelerated by cooling.

The adrenals also play a role in thermoregulation through the adrenaline that they secrete into the blood, which increases heat production by activating oxidation processes in the tissues, particularly in the muscles, and reduces heat loss through its vasoconstrictive effect. Adrenaline therefore is capable of raising body temperature (*adrenaline hyperthermia*).

## HYPOTHERMIA AND HYPERHERMIA

If a person is exposed to the effect of very high or very low temperatures for some time, the mechanisms of physical and chemical thermoregulation that maintain the constancy of body temperature under normal conditions become inadequate and overheating (*hyperthermia*), or cooling (*hypothermia*) of the body occurs.

The state of hypothermia develops when the temperature in the axilla falls below 35°C and is induced most rapidly by immersion of the body in cold water. Symptoms of sympathetic excitation are first encountered, attended by sharp reflex excitation of heat-generating processes, facilitated by the muscular contractions (shivering) that occur in cold. Some time after, body temperature falls, the condition resembling the general anaesthesia first described in 1862 by Walter who experimented on animals, and marked by loss of sensitivity, diminution of reflex reactions, and reduction of excitation of the nerve centres. Hypothermia is characterized by a sharply reduced metabolic rate, slow respiration and cardiac contractions, diminished stroke volume of the blood flow, and lowered arterial pressure (at a body temperature of 24° to 25°C being as low as 15 to 20 per cent of the initial level).

In recent years artificially induced hypothermia with cooling of the body to between 24° and 28°C is practiced in operating theatres where operations on the heart and central nervous system are performed. The idea behind the procedure is as follows: since the metabolism of the brain, and therefore its oxygen requirements, are reduced considerably in hypothermia, arrest of blood supply to that organ can be endured for a longer period (from 15 to 20 minutes

at a temperature of 25° or 28°C, instead of the three to five minutes tolerated at normal body temperature), which means that temporary cessation of heart activity and arrest of respiration and circulation is tolerated more easily in a state of hypothermia. The condition is relieved by warming the body, which must be done rapidly.

The initial activation of metabolism that occurs as an adaptational reaction to cooling is prevented in artificial hypothermia by the introduction of chemical preparations which block the conduction of impulses through the sympathetic ganglia (*ganglioplegics*) and arrest their transmission from the nerves to the skeletal muscles (*muscle relaxants*).

Hyperthermia develops when axilla temperature rises above 37°C, and is induced by prolonged exposure to the effect of high environmental temperature, particularly when the air is very humid and, consequently, sensible perspiration is reduced. Drastic hyperthermia with a body temperature of 40° to 41°C is attended with the grave general condition known as *heat stroke*.

Hyperthermia in which the elevation of body temperature is caused only by external factors has to be distinguished from conditions in which the change in temperature is due to disturbances in the thermoregulating process itself, with external conditions unaltered. *Fever* due to infection is the form most frequently encountered. The condition is the concern of pathology and not of physiology.

## Chapter 8

# EXCRETORY PROCESSES

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Excretory processes are the final link in metabolism within the organism; their immediate result is elimination of breakdown products that are of no further use to the organism. The excretory organs in man are the kidneys, sweat glands, lungs, and intestine.

The lungs are excretory organs because carbon dioxide, water, and certain volatile substances, e. g. the ether and chloroform vapours of anaesthetics and alcohol vapours from intoxication, are eliminated through them. The intestine excretes salts of heavy metals.

As well as eliminating end products of metabolism from the organism the excretory organs have a role in maintaining its internal environment in a constant state and condition. Thus they take part in the regulation of osmotic pressure, i. e. in keeping it constant (*isosmoticity*), and in maintaining a constant ion composition (*iso-ionia*) within the organism.

The kidneys, lungs, and sweat glands are also of major importance in keeping the concentration of hydrogen ions in the organism at a constant level.

Since evaporation of water from the surface of the skin and the alveoles of the lungs lowers body temperature, the sweat glands and lungs also have a thermoregulatory significance.

The sebaceous and mammary glands are an exception among the excretory organs. Their secretions, sebum and milk, are not end products of metabolism and have a definite physiological importance, milk as food for the newborn, and sebum as a lubricant for the skin.

## THE FUNCTION OF THE KIDNEYS

The kidneys eliminate various metabolites formed in the organism and also a great number of foreign and toxic substances taken into it from the external environment. They also perform a number of other functions, namely: control of the water balance, acid-base equilibrium, and of the balance of sodium, potassium, chloride, phosphorus, and other salts in the organism; the synthesis of certain chemical compounds; and the production of renin, a physiologically active substance that influences the level of arterial pressure. Their main function, however, is the formation of urine.

## THE NEPHRON AND ITS BLOOD SUPPLY

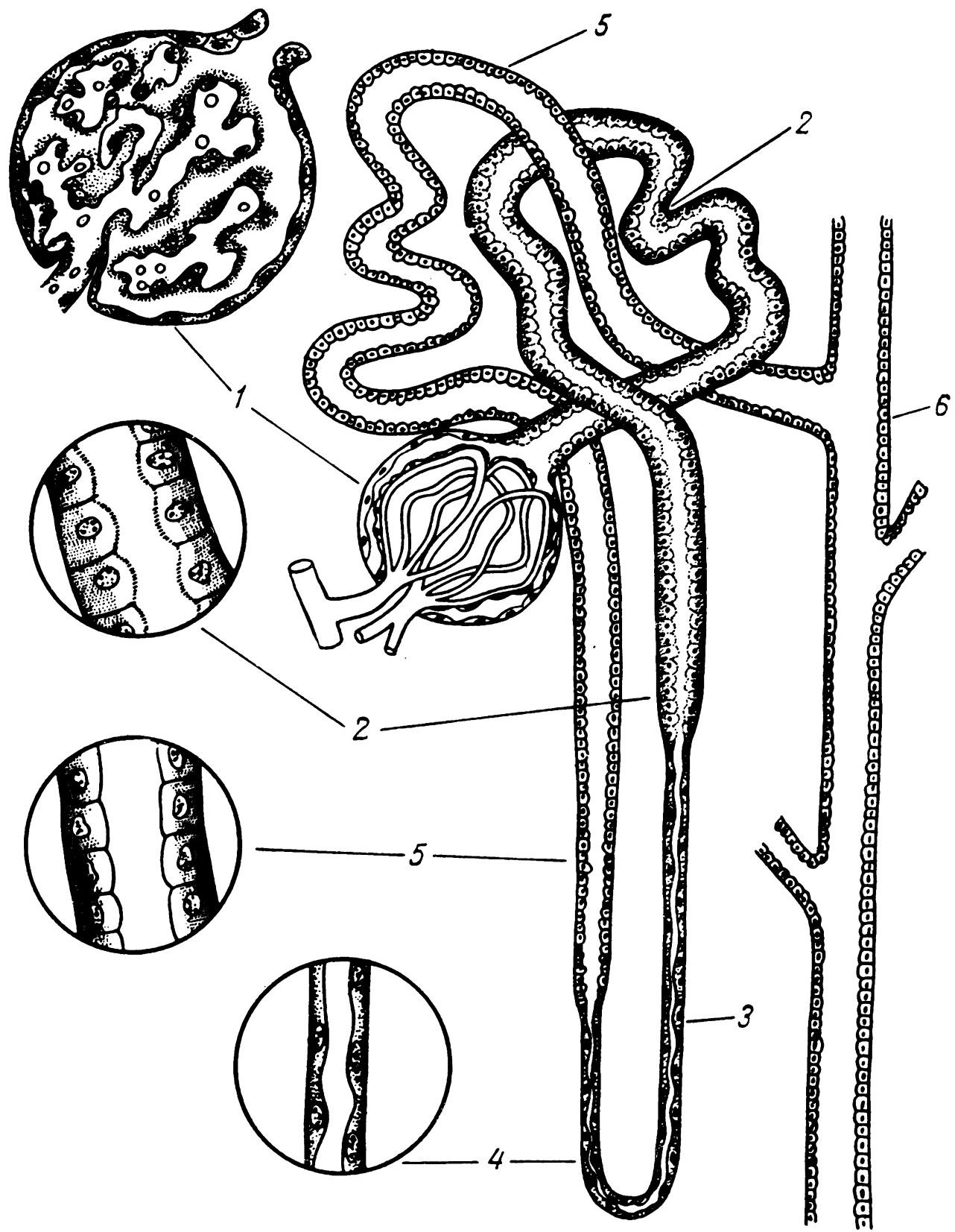
A kidney is a complex structure consisting of one million or so structural and functional units called *nephrons* (Fig. 98), separated by connective (interstitial) tissue.

A nephron is a functional unit because it accomplishes the entire complex of processes that result in the formation of urine.

Each nephron begins as a small capsule shaped like a bowl with double walls (the Shumlyansky-Bowman capsule) that contains a tuft of capillaries (or glomerulus). A glomerulus surrounded by a glomerular capsule is known as the *Malpighian* or *renal corpuscle*. Between the walls of the capsule there is a space from which tubules open. The internal lining of the capsule is made of fine flattened squamous epithelial cells which electron microscope research has shown to be separated by slits and to lie on a basement membrane consisting of three layers of molecules.

The endothelial cells of the capillaries of the Malpighian corpuscle have perforations about 0.1 micron in diameter. Thus, the only barrier between the blood in them and the cavity of the capsule is the thin basement membrane.

From the cavity of the capsule passes a uriniferous tubule. This tubule is coiled at the beginning (*proximal convoluted tubule*), but on reaching the boundary between the cortical and medullary substances narrows and becomes straight. In the medullary substance it forms the *loop of Henle*, and then returns to the cortical substance. In this way, Henle's loop consists of a descending (or proximal) and an ascending (or distal) portion or limb. In the cortical substance of a kidney, or on the boundary between the medullary and cortical substance the straight tubule again become coiled, forming the *distal convoluted tubule* which falls into an excretory duct, the *collecting tubule*. A great number of these collecting tubules join to form common excretory ducts which pass through the medullary



**FIG. 98. Diagram of the structure of a nephron (after Smith)**

1 — glomerulus; 2 — proximal convoluted tubule; 3 — descending limb of Henle's loop;  
4 — ascending limb of Henle's loop; 5 — distal convoluted tubule; 6 — collecting tubules.  
The structure of the epithelium in the different portions of the nephron is shown in the circles

substance to the apices of the renal papillae projecting into the pelvis of the kidney.

The diameter of each Shumlyansky-Bowman capsule is about 0.2 millimetre and the total length of the tubules of a single nephron is between 35 and 50 millimetres.

**Blood supply.** The renal arteries branch into smaller and smaller vessels to form arterioles. Each arteriole enters a Shumlyansky-

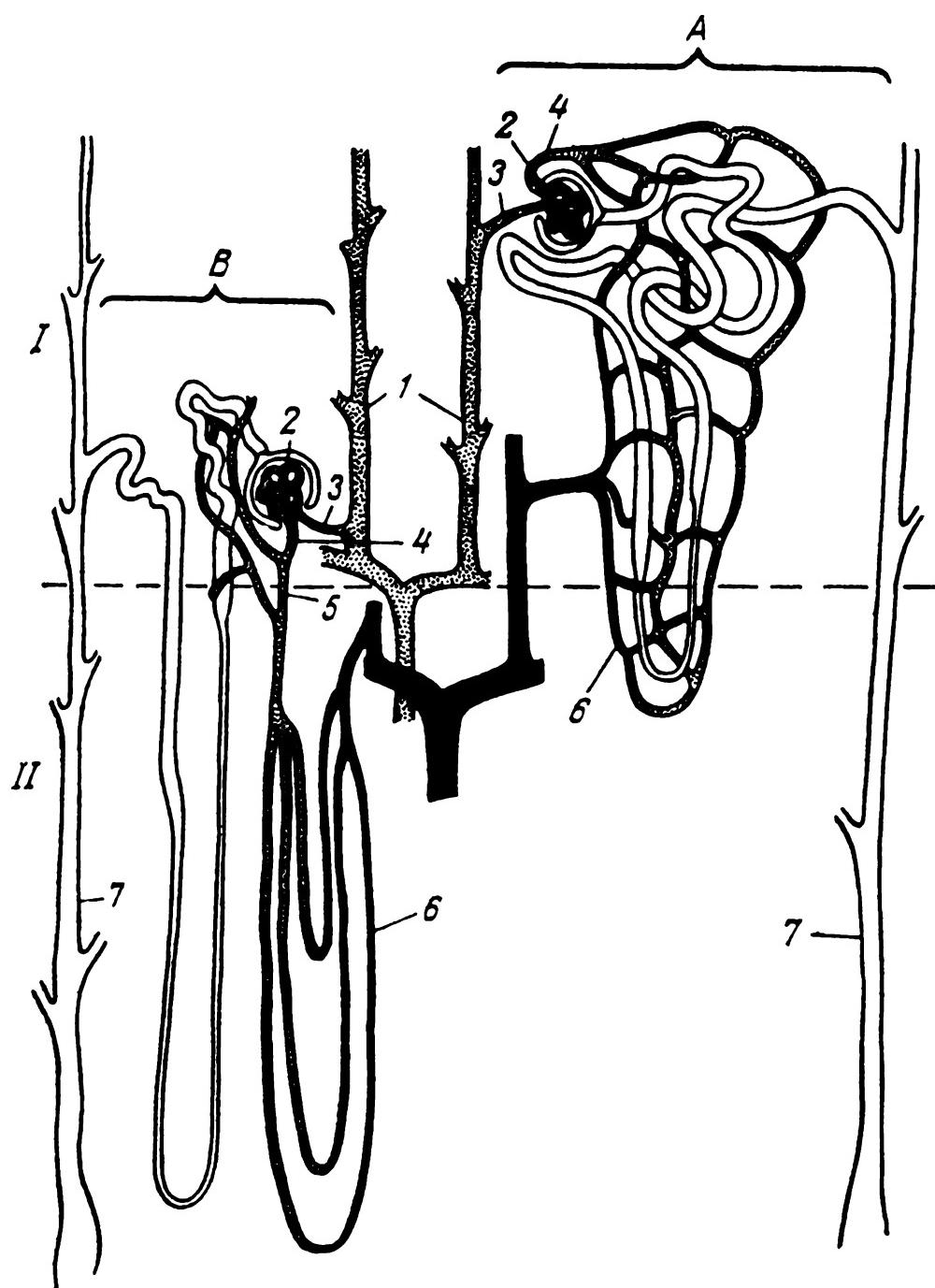


FIG. 99. Diagram showing the cortical (A) and juxta-medullary nephrons (B) and their blood supply (after Smith)

I — cortical substance of the kidney; II — medullary substance of the kidney; 1 — arteries; 2 — glomerulus and capsule; 3 — arteriole passing to the Malpighian corpuscle; 4 — arteriole leaving the Malpighian corpuscle and forming a capillary network around the tubules of the cortical nephron; 5 — arteriole leaving the Malpighian corpuscle of the juxta-medullary nephron; 6 — venules; 7 — collecting tubules

Bowman capsule and there divides into about fifty capillary loops which form the glomerular tuft.

Merging again, the capillaries form another arteriole which leaves the glomerulus. The arteriole that supplies the glomerulus with blood is called the afferent vessel (*vas afferens*), while that along which the blood flows from the glomerulus is known as the efferent vessel (*vas efferens*). The diameter of the efferent vessel is narrower than that of the afferent. Shortly after leaving the glomerulus, the efferent vessel again breaks up into capillaries and forms a dense network of capillaries twined about the proximal and distal convoluted tubules (Fig. 99A). Thus blood that has passed along the glomerular capillaries then flows through those of the tubular capillaries. Blood is supplied to the tubules as well by capillaries that arise from a small number of arterioles which do not form part of the Malpighian corpuscle.

From the capillary network of the tubules blood enters small veins which merge forming the arciform veins (*venae arcuatae*), which in turn join to form the renal vein that drains into the inferior vena cava.

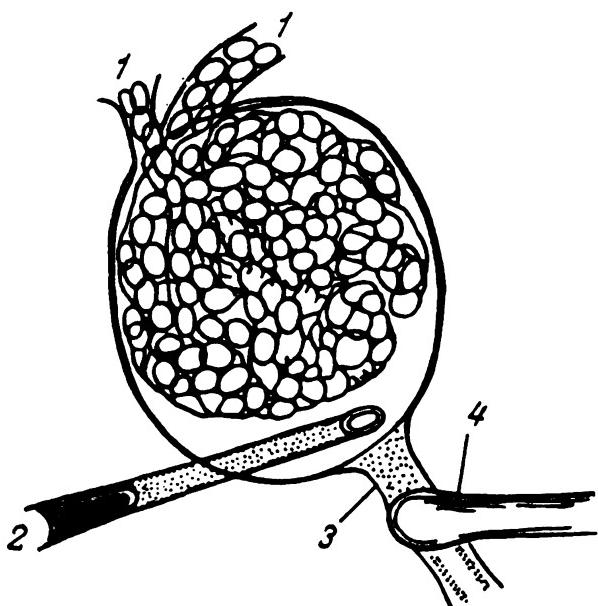
**The juxta-medullary nephrons.** It has not long been revealed that, in addition to the nephrons described above, the kidneys also contain other, juxta-medullary, nephrons differing from them in localization and blood supply. These nephrons are almost entirely confined to the medullary substance. Their glomeruli lie between the cortical and medullary substance and Henle's loop, on the boundary with the renal pelvis.

The blood supply of a juxta-medullary nephron differs from that of a cortical one in that the diameters of its efferent and afferent vessels are equal. The efferent arteriole does not form a capillary network around the tubules but drains into the venous system after a certain distance (Fig. 99B).

**The juxta-glomerular apparatus.** The afferent arteriole has a thickening in its wall where it enters the glomerulus formed by myoepithelial cells, and known as the *juxta-glomerular apparatus* (adjacent to a glomerulus). The cells of this apparatus have internal secretion function, producing renin (p. 154) when blood flow to the kidneys is reduced. Renin is concerned in the regulation of arterial pressure and apparently has significance for maintaining a normal balance of electrolyte.

#### GLOMERULAR FILTRATION

By 1844 Ludwig had assumed on the basis of his research that the process of urine formation consisted in *filtration*, which occurred through the walls of the glomerular capillaries, and *reabsorption*



**FIG. 100.** Diagram showing the method for collecting glomerular filtrate with a micropipette (after Richards)  
 1 — blood vessels; 2 — micro-pipette;  
 3 — tubule; 4 — glass rod obstructing flow of urine from the capsule

which took place in the tubules. This assumption was modified by Cushny who formulated the *filtration-reabsorption theory of urine formation* that underlies the modern conceptions. This theory has been confirmed by a large number of experiments.

The current theory is that water and all substances dissolved in the plasma, with the exception of macromolecular compounds, are filtered into the glomerular capsule from blood flowing along the glomerular capillaries. In the glomeruli filtration occurs through the endothelial perforations, the basement membrane, and the slits between the epithelial cells of the internal capsular wall. This filter is permeable to molecules with diameter around 100 Angstroms, but does not allow passage of larger particles with molecular weights above 70,000. Therefore macromolecular proteins, like globulins (the molecular weight of which exceeds 160,000) are not encountered in the filtrate.

Certain foreign proteins which have a relatively low molecular weight (egg-white, gelatin, etc.) pass through the renal filter and are eliminated in the urine. Plasma albumins, which have a molecular weight around 70,000, pass into the filtrate in negligible quantities (less than one per cent of their total content in the plasma). In cases of intravascular haemolysis, i. e. of breakdown of erythrocytes with the release of haemoglobin molecules (molecular weight 68,000) into the plasma, only 5 per cent of the haemoglobin passes into the filtrate. Inorganic salts and low-molecular organic compounds (urea, uric acid, glucose, amino acids, etc.) pass easily into the capsule.

Direct evidence of this was obtained in the acute microphysiological experiments made by Richards, first on frogs and later on mammals (guinea-pigs and rats). The kidney was exposed and a

very fine micropipette was introduced into one of the capsules lying near the surface (Fig. 100), which could be seen under a microscope with low magnification. The tubule leading from the capsule was compressed to stop the flow of the fluid, which permitted an adequate volume of filtrate to be collected in the micropipette and examined for its composition. It was found that the content of inorganic and organic substances in the *glomerular filtrate* (with the exception of proteins) was the same as in the plasma.

The quantity of glomerular filtrate formed is very great, amounting to 150 or 170 litres a day. This large filtration capacity is possible because of the rich blood supply to the kidneys, the peculiar structure and large filtration surface of the glomerular capillaries, and the relatively high blood pressure within them, which may be illustrated by the following data: 1,700 litres of blood pass through the kidneys during a day, so that about one litre of filtrate is formed from every six to ten litres of blood flowing along the glomerular capillaries. The total surface of the capillaries involved is between 1.5 and 2 square metres, i. e. is equal to the surface area of the body. The blood pressure in the glomerular capillaries is about 70 millimetres of mercury; this relatively high value is due to the renal arteries rising directly from the abdominal aorta and to the fairly short distance between them and the glomeruli. It is also conditioned by the fact that the diameter of the efferent artery is about half that of the afferent.

The role of blood pressure in urine formation was shown by the middle of the last century in Ludwig's laboratory, where it was demonstrated on a dog that the flow of urine from a catheter inserted into a dissected ureter diminished, or ceased entirely, when the blood pressure was lowered by blood-letting. Glomerular filtration, however, is determined not only by the blood pressure in the capillaries, but also by the oncotic pressure of the blood plasma which opposes escape of fluid from the blood stream (p. 63) and by the hydraulic pressure of the filtrate that fills the capsule and tubules. The blood pressure in the capillaries of the glomeruli is the force that effects filtration, while the oncotic pressure and the pressure of the urine in the capsule counteract it; hence glomerular filtration occurs only when the blood pressure in the capillaries exceeds the sum of the pressures of the two opposing forces. The oncotic pressure of the blood plasma is approximately 30 millimetres and the pressure produced by the filtrate in the capsule and tubules is about 20 millimetres mercury; therefore the pressure responsible for glomerular filtration averages 70 mm -- (30 mm + 20 mm) = 20 mm of mercury. Thus it is clear why the formation of urine ceased in Ludwig's experiments as soon as the blood pressure in the renal artery dropped below the level that ensured the necessary filtration pressure.

The results of Ustimovich's experiments can be explained in the same way; he showed that the formation of urine ceased when intrarenal pressure was raised artificially to a level of 30 or 40 millimetres mercury.

**Determination of the amount of fluid filtration in the glomeruli.** Smith showed that the quantity of glomerular filtrate can be determined in man by introducing a substance into the blood that filters easily through the wall of the glomerular capillaries and is eliminated from the organism in the urine without undergoing any change while passing along the tubules. The content of the substance in the urine will thus be equal to that in the glomerular filtrate.

Such a substance is the fructose polysaccharide *inulin* (molecular weight about 5,000), whose free passage into the filtrate was proved experimentally by Richards by micropunctures of the glomeruli. (In that way he showed that the inulin concentration in the filtrate in the capsules was equal to that in the blood plasma.)

Knowing the inulin concentration of the plasma, which is equal to that of the glomerular filtrate ( $P_{in}$ ), the amount of urine eliminated during the experiment ( $V$ ), and the concentration of inulin in it ( $U_{in}$ ) one can easily determine the total volume of filtrate ( $F$ ). Since the amount of inulin present in the urine ( $V \cdot U_{in}$ ) is equal to the amount that passed into the filtrate ( $F \cdot P_{in}$ ), we find from the equation obtained

$$F \cdot P_{in} = V \cdot U_{in} \text{ that } F = \frac{V \cdot U_{in}}{P_{in}}.$$

Having determined the amount of filtration occurring over a certain period, we can then calculate the volume per minute, which is normally 120 millilitres for both kidneys.

This value shows the volume of plasma that has been cleared of inulin in one minute, and is referred to as the *plasma clearance for inulin*.

The plasma clearance for other substances can be determined in the same way; its value is lower for substances that pass into the glomerular filtrate but are reabsorbed in the tubules than it is for inulin, which does not undergo reabsorption. The clearance for substances that are not only filtered through the glomerular capillaries but are also secreted by the tubular epithelium is higher than for inulin, so that a larger volume of blood can be cleared by the kidneys per unit of time.

The clearance test is employed clinically to estimate renal function.

#### TUBULAR REABSORPTION

Water, and a number of substances dissolved in it, undergoes *reabsorption in the tubules*.

The tubules are long thin tubes, with a very great total length, between 70 and 100 kilometres. They are lined with epithelium, which varies in structure in their different parts; in the proximal convoluted tubules the epithelium is columnar, in the descending limb of Henle's loop it flattens out, and becomes cuboidal in the ascending limb (Fig. 98). In the distal convoluted tubules it is also cuboidal.

The free surface of the columnar cells in the lumen of the tubules has a striated border, which has been shown under the electron microscope to be formed by microvilli. Thus the total surface-area of the tubules is increased to 40 or 50 square metres. There are also microvilli in the loop.

The extensive total surface of the tubules explains their large reabsorption capacity. Only 1.0 or 1.5 litres of the 170-litre daily volume of glomerular filtrate is eliminated in the form of *final urine*. The remaining fluid and much of the matter dissolved in it are absorbed in the tubules and pass into the renal tissue fluid and the blood.

Richards introduced two micropipettes into the tubules, which permitted certain solutions to be injected into the proximal part of a convoluted tubule and fluid to be collected from the lower, distal portion for examination. The experiments demonstrated that water and a number of substances are actively reabsorbed into the blood from the urine while it is passing along the tubule.

The reabsorption of certain substances is governed by their concentration in the blood. Thus glucose is reabsorbed completely if its concentration in the plasma is not above 150 to 180 milligrams per cent; with a higher concentration only partial absorption occurs and glucose appears in the urine (*glycosuria*). This underlies the hypothesis of an elimination threshold for various substances.

The *elimination threshold* is that concentration of a substance in the blood at which it cannot be reabsorbed completely in the tubules and so passes into the final urine. It varies for different "threshold" substances. Other, no-threshold, substances are not reabsorbed and are eliminated with the urine whatever their concentration in the blood, even if very small. Examples are creatinine and inulin. Glucose, which is completely reabsorbed if its concentration in the blood is normal, is an example of a threshold substance. Many amino acids and vitamins, plasma proteins that have passed into the filtrate, most of the sodium, potassium, calcium, and chloride ions, and other substances are also completely reabsorbed in the tubules. Thus, substances needed by the body are reabsorbed, while final products of metabolism eliminated from the body, such as urea, uric acid, and ammonia, are reabsorbed in much smaller amounts; some (sulphates, creatinine) are not reabsorbed at all but are discharged in the urine.

The proportions of the various substances in human plasma, glomerular filtrate, and final urine are shown in the following table (after Cushny).

Substance	Percentage content		Ratio of content in urine and plasma
	Blood plasma and glomerular filtrate	Urine secreted into the ureters	
Urea	0.03	2.0	65:1
Uric acid	0.004	0.05	12:1
Glucose	0.1 – 0.15	—	Absent from urine
Potassium	0.02	0.15	7:1
Sodium	0.32	0.35	Approximately equal
Phosphates	0.009	0.15	16:1
Sulphates	0.002	0.18	90:1

**Determination of reabsorption in man.** The amount of any substance reabsorbed can be estimated by injecting it intravenously, determining its concentration in the urine and blood, and measuring the amount of urine eliminated. Inulin is introduced into the blood at the same time to determine the volume of glomerular filtration.

The reabsorption of substances that normally occur in the urine and blood (urea, for example) can be estimated without infusing them into the blood; it is sufficient to determine their concentration in the blood plasma and eliminated urine, and the total amount of urine.

To determine the reabsorption maximum of glucose, it has to be injected into the blood and its concentration raised above the threshold level so that it appears in the urine. The following calculation is made.

The amount of glucose passing into the filtrate per minute is equal to its concentration in the plasma ( $P_g$ ) multiplied by the volume of filtrate formed per minute ( $F$ ), i. e.  $F \cdot P_g$ . The amount of glucose reabsorbed in the tubules ( $R$ ) will be equal to the difference between the amount of glucose in the filtrate and the amount in the urine:  $R = F \cdot P_g - V \cdot U_g$ , where  $U_g$  is the concentration of glucose in the urine, and  $V$  is the amount of final urine produced by the kidneys per minute.

As already shown, there will be no glucose in the urine if  $P_g$  is less than 160 to 180 milligrams per cent, that is, when  $V \cdot U_g = 0$ ; consequently, the glucose is completely reabsorbed ( $R = F \cdot P_g$ ).

The mechanism of reabsorption varies with the substance. The reabsorption of sodium, glucose, amino acids, and certain other substances, for instance, is due to active vital processes, while the absorption of water and chlorides occurs passively by the laws of diffusion and osmosis.

Evidence of active transport of certain substances was obtained in experiments on an isolated dog kidney. Cyanide poisoning of the kidney, leading to paralysis of the oxidation processes, cooling of the kidney, resulting in a reduced metabolic rate, reduced reabsorption and sharply increased the amount of urine excreted. The fact that this occurred in cooling, in spite of the constriction of the renal vessels and the decrease of filtration, deserves attention.

Owing to the activity of the columnar epithelium in the renal tubules, substances may be absorbed in the direction opposite to their concentration gradient, that is, when their concentration in the blood is equal to or higher than their concentration in the tubular fluid.

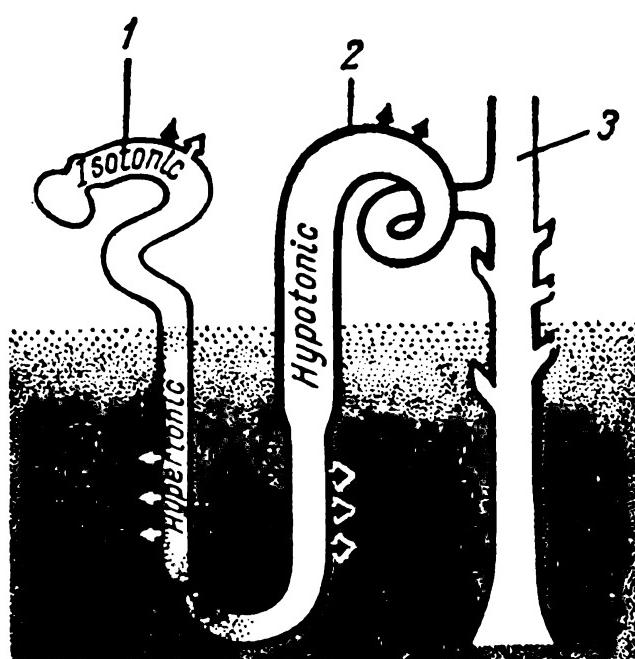
Ginetsinsky and others have shown that an important role in the reabsorption of sodium ions is played by an enzyme, succinic dehydrogenase, which is present in all cells concerned in the transport of sodium ions. Suppression of its activity by mercury preparations hinders the absorption of sodium salts.

Active transport of sodium ions through the tubular epithelium also induces passage of chlorine ions, owing to the forces of electrostatic interaction; the positively charged sodium ions carry negatively charged chlorine ions, and certain other anions, along with them.

Water is absorbed in great quantities, the process occurring passively through the laws of diffusion and osmosis. The absorption of glucose, sodium, potassium, calcium, and other substances from the glomerular filtrate into the renal tissue fluid and blood raises the osmotic pressure of the tissue fluid and lowers the osmotic pressure of the filtrate which becomes hypotonic. Owing to difference in osmotic pressure water passes from the filtrate to the tissue fluid and blood. This passive process occurs parallel with the active transport of organic and inorganic compounds.

The passage of water brings the osmotic pressure of the filtrate in the proximal convoluted tubules up to the level of that of the tissue fluid and blood. In this way the filtrate remains isotonic in spite of the copious absorption of salts. The isotonicity of the filtrate is impaired in Henle's loop by the activity of a peculiar mechanism known as the *counter-current system*.

**Functions of Henle's loop.** The essence of the counter-current system is that both the descending and ascending limbs of the loop are in close contact and function jointly as a single mechanism (Fig. 101). The epithelium of the descending (proximal) limb is permeable to water but not to sodium ions; that of the ascending



**FIG. 101.** Diagram illustrating the work of the counter-current system (after Best and Taylor)

The darkened background shows the degree of concentration of urine and tissue fluid. The white arrows indicate the passage of water, the black arrows, the passage of sodium ions. 1 — proximal convoluted tubule continuous with the proximal limb of the loop; 2 — distal convoluted tubule emerging from the distal limb of the loop; 3 — collecting tubule

(distal) limb is capable of active reabsorption of sodium ions, that is, it conveys these ions from the tubular urine to the renal tissue fluid, but at the same time does not permit passage of water from the tubular lumen to the tissue fluid.

While passing along the descending (proximal) limb of the loop of Henle, the urine is gradually concentrated as water passes into the tissue fluid. The passage of water is a passive process that occurs because the epithelium of the adjoining ascending (distal) limb actively reabsorbs sodium ions, i. e. effects their passage from the tubular lumen to the tissue (interstitial) fluid; the sodium ions in the tissue fluid then attract water molecules not from the distal tubule but from the proximal.

The escape of water from the lumen of the proximal tubule leads to progressive thickening of the urine, till it attains maximal concentration at the bend of the loop. This high concentration facilitates the passage of sodium ions from the distal limb since its walls are impermeable to water but actively reabsorb the sodium. Their passage in turn increases the osmotic pressure of the fluid, which promotes escape of water from the proximal limb, as already pointed out. Thus the passage of water from the urine in the proximal limb facilitates sodium reabsorption in the distal limb, while the reabsorption of sodium in turn facilitates passage of water from the proximal limb. The two processes are coupled. As a consequence of the passage of sodium the tubular fluid, which is hypertonic at the bend of the loop, becomes isotonic or even hypotonic to the blood plasma at the end of the ascending limb.

The difference between the osmotic pressures of the urine in the contiguous limbs at a given level is slight, while the osmotic pressure of the tissue fluid surrounding the tubules is approximately equal to that of the urine in any portion of their limbs.

The osmotic pressure of the fluid in the descending limb gradually increases owing to the absorption of water, while that of the fluid in the ascending limb diminishes because of the reabsorption of sodium. Thus, though the pressure difference between two adjacent areas of the proximal (or distal) limb is slight, these small falls in pressure are aggregated along the length of the loop, so that the pressure gradient between the initial (or terminal) portion of the loop and its end is considerable. It also needs to be stressed that a large amount of urine isotonic with the blood enters the initial portion of the loop. Although a great quantity of water and sodium is lost in Henle's loop so that the volume of urine flowing from the loop is considerably reduced, it is again isotonic or even hypotonic to the blood plasma. The loop therefore acts as a concentrating mechanism by which large amounts of water and sodium ions are reabsorbed. The principle of the counter-current system, as described above, is used in engineering when large differences of concentration have to be produced.

The absorption of sodium and potassium ions, water, and other substances continues in the distal convoluted tubule, but the volume of reabsorption of salts ( *facultative reabsorption*) varies, in contrast to the proximal convoluted tubule and Henle's loop where it is constant ( *obligatory reabsorption*). In the distal convoluted tubule reabsorption depends upon the level of sodium and potassium ions in the blood and is an important regulating mechanism maintaining a constant concentration of these ions in the organism (see below, p. 352).

**Function of the collecting tubules.** A great amount of watery urine drains from the renal tubules into the collecting tubules where it undergoes concentration, so that only 1.0 to 1.5 litres of urine enters the renal pelvis daily. Concentration of the hypotonic urine entering the collecting tubules is mainly effected by the absorption of water.

Water is reabsorbed because the collecting tubules, whose walls are permeable to water, pass through the medullary layer of the kidneys where the osmotic pressure of the tissue fluid is high, so that water escapes from their lumina into the interstitial fluid.

#### THE SECRETORY FUNCTION OF THE TUBULES

Certain colloidal dyes, introduced into the blood, appear in the urine although they cannot penetrate the glomerular wall. Histological research has shown that they are not present in the capsular fluid but occur in the lumina of the tubules and in the protoplasm of their epithelium. This has led to the conclusion that the tubular epithelium possesses secretory, as well as a reabsorption, function.

Tubular secretion results from an activity of the epithelial cells that is associated with intensive metabolic processes. Its reduction

when tissue respiration is inhibited by cyanides proves this. The introduction of dinitrophenol, which blocks the formation of high energy-yielding phosphorus compounds (adenosine triphosphoric acid, etc.), also arrests secretion.

In higher animals and man tubular secretion apparently contributes little to the volume of urine formed, but in certain reptiles and birds it is the main mechanism of urine formation since their kidneys contain only a few glomeruli and most of the tubules have blind endings.

Owing to the secretory function of the tubules substances that do not undergo glomerular filtration are eliminated from the organism.

According to data obtained in Orbeli's laboratory, the secretory mechanism may also take part in the elimination of urea when the level of the latter increases in the blood. Tubular secretion would seem to serve as a reserve mechanism of urine formation ensuring elimination of breakdown products.

**Determination of the volume of tubular secretion in man.** The secretory function of the tubules may be measured quantitatively by injecting substances into the blood that are mainly excreted from the organism through tubular secretion, such as diodrast, the sodium salt of para-aminohippuric acid, and certain others. Any one of them is introduced intravenously together with inulin (which permits the volume of glomerular filtration to be determined, as described above.)

The total amount of diodrast in the urine is equal to  $V \cdot U_d$  (where  $U_d$  is the urinary diodrast concentration, and  $V$  is the volume of urine formed in a definite interval of time). It is the sum of the amount of diodrast that has passed into the urine by glomerular filtration ( $F \cdot P_d$ , where  $F$  is the volume of filtration determined by inulin, and  $P_d$  is the diodrast concentration in the filtrate equal to its concentration in the blood plasma), and the amount of diodrast secreted by the tubular epithelium ( $S$ ). Expressing these relations by the equation  $V \cdot U_d = F \cdot P_d + S$ , we find that  $S = V \cdot U_d - F \cdot P_d$ .

**Determination of the volume of the renal blood flow.** This involves the infusion of para-aminohippuric acid or diodrast into the blood. These substances are completely cleared from the blood when it flows through the kidneys for the very first time, which explains why they are only present in the arterial blood flowing to the kidneys and are absent from the venous blood flowing away from them.

The volume of plasma flowing through the kidneys within a unit of time can be determined if the amount of a substance eliminated in the urine and its concentration in the plasma are known. Let us take an example of the calculation. The amount of para-aminohippuric acid excreted with the urine ( $V \cdot U_{pah}$ , where  $V$  is the volume of urine passed within the given interval of time, and

$U_{pah}$  is the concentration of the acid in the urine) is equal to the amount brought to the kidneys ( $C \cdot P_{pah}$ , where  $C$  is the volume of the plasma flowing through the kidneys within the given interval of time, while  $P_{pah}$  is the concentration of para-aminohippuric acid in the plasma). From the equation  $V \cdot U_{pah} = C \cdot P_{pah}$  we find that:

$$C = \frac{V \cdot U_{pah}}{P_{pah}}.$$

The amount of blood passing through the kidney within a unit of time can easily be estimated by determining the percentage of the plasma and formed elements in the blood.

Para-aminohippuric acid is preferable to diodrast for such studies because its clearance is higher and the estimate of plasma flow more accurate.

Renal plasma flow averages 650 millilitres per minute and the blood flow, 1,200 millilitres per minute. Having measured the volume of filtration by injection of inulin, and the volume of the plasma flow by para-aminohippuric acid, we will find that the volume of the filtrate in the glomeruli is about 20 per cent that of the plasma flowing through the kidneys.

#### THE ROLE OF THE KIDNEYS IN THE SYNTHESIS OF SUBSTANCES FOUND IN URINE

Apart from the elimination of metabolic products brought to them by the blood (urea, uric acid, indican, urobilin), the kidneys themselves form certain substances, hippuric acid, ammonia, etc. that pass into the urine.

*Hippuric acid* is formed in the epithelium of the renal tubules from benzoic acid and the amino acid glycocoll. Its formation by the renal tissue has been proved in experiments on isolated kidneys: hippuric acid appears in urine flowing from the ureter of an isolated kidney if a nutrient solution containing benzoic acid and glycocoll is perfused through its vessels.

Ammonia is formed in the tubular epithelium from amino groups released on deamination of amino acids, mainly from the naturally occurring compound glutamine. Evidence of the formation of ammonia in the kidneys is the fact that its content in the blood of the renal vein is two or three times that in the blood flowing in the renal artery and in the blood draining from other tissues.

Renal tissue is rich in enzymes and is the site of a number of other chemical processes among which the splitting of sulphates and phosphates from certain sulphur- and phosphorus-containing organic compounds should be mentioned.

## ROLE OF THE KIDNEYS IN MAINTAINING A CONSTANT COMPOSITION OF THE INTERNAL MEDIUM

**Role of the kidneys in water balance and control of blood osmotic pressure.** When water and salts enter the body in large amounts they are mainly eliminated by the kidneys, which thus help to restore the normal osmotic pressure of the blood. If the excess supply occurs very rapidly, through intravenous infusions for example, the water and salts first pass into the tissues (mainly into the skin and muscles) and are then gradually excreted from the organism by the kidneys. The increase in urine formation leading to the elimination of excess amounts of water and salts is known as *dilution diuresis*. Its high intensity is attributed to the effect of several regulatory mechanisms.

The introduction of fluids into the vascular system raises arterial pressure and, consequently, the filtration pressure in the glomeruli, so that the rate of filtration and the amount of urine excreted increase. The raised blood pressure in the vessels stimulates the pressoreceptors in the vascular system, which in turn causes a reflex decrease in the tone of the arterioles. Flow of blood along the afferent glomerular arteries is stimulated; filtration and, consequently, diuresis increase. A rise in the amount of fluid in the blood increases the extent of atrial filling and is followed by a reflex intensification of urine excretion (p. 129).

The introduction of hypertonic or hypotonic solutions into the blood changes its osmotic pressure, which also alters urine excretion. The mechanism of the reaction is complex; an important part is played by the *osmoreceptors* located in the diencephalon (in the supra-optic nucleus of the hypothalamus). An osmoreceptor is a highly differentiated nerve cell which has in its body a vacuole filled with intracellular fluid with an osmotic pressure equal to that of the tissue fluid and blood. When the osmotic pressure of the blood and tissue fluid is raised water escapes from the osmoreceptor vacuole into the tissue fluid under the effect of osmosis, as a result the vacuole and the body of the osmoreceptor cell shrink which results in faster generation of nerve impulses and causes increased secretion of *antidiuretic hormone* by the pituitary gland (p. 406). This hormone, acting upon the kidneys, causes an increase in the reabsorption of water into the blood from the fluid in the collecting tubules, with the result that the urine excreted is more concentrated. In this way the organism gets rid of excess salts with little loss of water, which reduces the osmotic pressure of the blood.

With the *hydraemia* (increase in blood water content) that follows from excess drinking of water or from the infusion of a hypotonic solution into the blood, secretion of the antidiuretic hormone falls because the drop in the osmotic pressure of the blood and tissue fluid causes water to pass into the vacuoles of the osmoreceptors and enlarges these cells. There is also a fall in the frequency of im-

pulses reaching the pituitary from the osmoreceptors and in the secretion of the antidiuretic hormone. As a result absorption of water from the urine declines and the kidneys excrete greater amounts of dilute urine; thus the excess water is eliminated from the organism.

A change in blood osmotic pressure has a direct effect on the process of water reabsorption in the tubules, which is why diuresis may be produced by the introduction of *no-threshold substances* (p. 343), sulphates, for example, or creatinine. Owing to their osmotic pressure they retain a certain amount of water in the tubules and prevent its reabsorption, so that secretion of urine is augmented.

This phenomenon is referred to as *tubular diuresis*. It may also be induced by intravenous injection of threshold substances that are reabsorbed in the tubules when their content in the blood exceeds the threshold. Glucose is an example. If the blood glucose level is raised above its threshold, the amount of glucose that cannot be absorbed by the tubules enters the urine, facilitating the elimination of larger volumes of water. Thus urinary excretion is augmented, its volume being in direct proportion to the super-threshold concentration of blood glucose. This is one of the reasons why diabetes mellitus is attended not only with elimination of sugar in the urine (*glycosuria*) but also with an increase in the volume of urine (*polyuria*).

**The role of the kidneys in controlling blood pH.** Renal activity is of significance in maintaining a constant concentration of hydrogen ions and eliminating the acid metabolites formed in the organism as a result of oxidation processes. The reaction of the urine is less constant than that of the blood; urine pH varies between 4.7 and 6.5, while the blood pH is 7.36. Urine becomes acid as it passes along the renal tubules because the threshold of sodium bicarbonate reabsorption is much higher than that of phosphate reabsorption. As a result the fluid in the tubules loses most of its sodium bicarbonate and the predominant acid phosphates make it acid.

With a meat diet, which causes the formation of various acids in the organism, the urine becomes more acid, while with an alkaline vegetable diet its reaction shifts toward alkalosis. The acidity of urine also increases during physical exercise because lactic and phosphoric acids form in abundance in the muscles and pass into the blood.

Renal regulation of blood pH depends considerably on the following: with a decline in the alkaline reserve of the blood (*acidosis*) the kidneys secrete urine containing  $\text{NaH}_2\text{PO}_4$ , that is, more acid urine; with alkalosis the urine contains  $\text{Na}_2\text{HPO}_4$ , that is, is more alkaline.

The synthesis of ammonia in the kidneys is of great importance for maintaining a constant hydrogen ion concentration in the blood

and neutralizing acid metabolites. Ammonia binds the acid radicals eliminated in the urine, replacing the sodium and potassium and forming ammonium salts of the non-volatile acids, which facilitates retention of sodium and potassium ions in the organism.

**Role of the kidneys in controlling the ion composition of blood.** The kidneys also play a big part in maintaining a constant proportion of sodium, potassium, calcium, phosphorus, and other ions in the blood and tissue fluid.

The epithelium of the distal convoluted tubules have an important role in this regulation. In the proximal portions of the nephron (in the proximal convoluted tubules and Henle's loop) variations in the level of sodium ions in the blood have little effect on sodium reabsorption, but in the distal portions (the distal convoluted tubules) they have considerable influence. When the amount of sodium in the plasma is deficient its facultative reabsorption in the distal portions increases sharply, while the reabsorption of potassium falls off correspondingly. As a result, the sodium content of the blood increases, its potassium content decreases, and their disturbed ratio returns to normal. Reverse phenomena occur when there is excess sodium in the blood; reabsorption in the second tubules is inhibited, while the reabsorption of potassium is correspondingly augmented, and the normal ratio of ions is re-established.

Thus, the kidney not only controls the level of sodium ions in the blood but also maintains the ratio of sodium and potassium ions.

The intensity of facultative sodium reabsorption is regulated by hormones secreted by the adrenals, in particular by aldosterone (p. 388).

The secretory function of the kidneys is also concerned in regulation of the blood content of other ions (calcium, phosphorus, chlorine).

**Role of the kidneys in controlling arterial pressure.** When renal blood supply is impaired, the enzyme renin is formed in the juxtaglomerular apparatus, as has already been pointed out (p. 154). Renin acts upon hypertensinogen, one of the plasma globulins, and converts it to hypertensin, a polypeptide consisting of ten amino acid residues, which causes constriction of the arterioles, thus raising arterial pressure. Hypertensin also affects urine secretion; its vasoconstrictive influence on the efferent glomerular arterioles raises their filtration pressure and thus increases urine formation.

#### CONTROL OF KIDNEY ACTIVITY

**Hormonal control.** If an animal's kidney is transplanted to its neck in such a way that it has no nervous connections with the body, and the renal artery is anastomosed with the carotid and the renal vein with the jugular vein, the kidney can function for weeks and months, excreting more or less normal urine. An excess intake

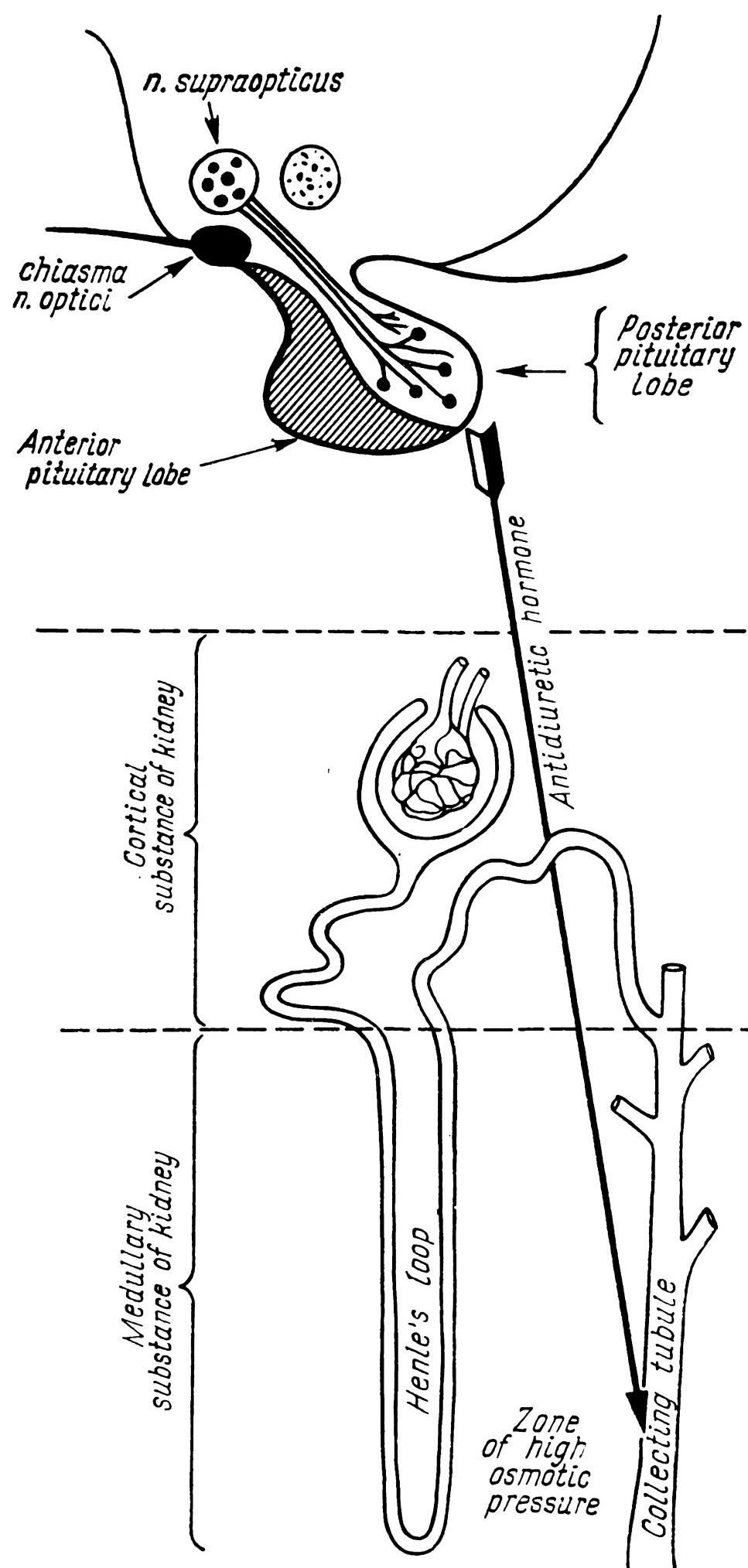


FIG. 102. Diagram illustrating the influence of the hypothalamus on the secretion of urine

of water or common salt increases the amount of water or salt eliminated by the transplanted kidney. Consequently even total denervation scarcely impairs normal renal function; furthermore, stimuli acting on the nervous system cause changes in the activity of the transplanted kidney. Thus, a denervated kidney, like a normally innervated one, ceases to excrete urine under the effect of pain stimuli. This is due to the fact that pain stimulates the hypothalamus. Impulses from the supra-optic nucleus are transmitted to the posterior pituitary lobe, causing an increase in secretion of the antidiuretic hormone (Fig. 102), which enters the blood and intensifies the reabsorption of water with a resultant decrease in diuresis (hence its name).

The way the antidiuretic hormone acts was revealed by Ginetsinsky. It raises the permeability of the walls of the collecting tubules so that water passes from the urine into the tissue fluid of the renal medulla and into the blood. The increase in the permeability of the tubules occurs under the influence of an enzyme hyaluronidase, which depolymerizes hyaluronic acid, a constituent of the intercellular matter of the tubular walls. As a result, the tubules become porous and permeable to water. Hyaluronidase is activated or formed by the epithelium of the tubules under the action of the antidiuretic hormone, which thus promotes the absorption of water.

The introduction of hyaluronidase preparations into the artery of a dog's kidney causes a sharp decrease in its urinary secretion, though excretion in the other kidney remains normal. The inhibitors of hyaluronidase (heparin, ascorbic acid) are antagonists of the antidiuretic hormone and sharply increase elimination of water in the urine.

Deficiency of the posterior pituitary lobe which secretes the antidiuretic hormone suppresses the effect of the mechanism just described. The walls of the distal portions of the nephron become completely impermeable to water and great amounts are passed in the urine. In such cases (*diabetes insipidus*) the daily output of urine may be as high as 20 or 25 litres. The secretion of the pituitary antidiuretic hormone is controlled by the hypothalamic nuclei.

Adrenaline, the hormone secreted by the adrenal medulla, also affects urinary secretion. The volume of the kidney grows if small doses are injected into its vessels. The explanation is that adrenaline causes constriction of the efferent arterial vessels (*vas efferens*), and thus leads to an increase in glomerular filtration pressure. Large doses of adrenaline also constrict the afferent vessels, which reduces blood flow to the glomeruli and suppresses diuresis.

Certain hormones known as mineralocorticoids, secreted by the adrenal cortex (aldosterone, desoxycorticosterone), act upon the tubular epithelium and promote the absorption of sodium into the blood. Disease of the adrenals or their resection abolishes this

mechanism and gives rise to marked loss of sodium in the urine and to severe disturbances in the organism.

The thyroid and parathyroid hormones also influence renal activity.

The hormone of the thyroid gland disturbs the binding of water and salts by the tissues, causing them to pass into the blood, and so causes an increase in urine secretion. At the same time, it intensifies all types of metabolism, protein metabolism in particular (causing an increase in the formation of its end products), which also leads to an increase in urinary secretion. The parathyroid hormone facilitates the passage of calcium and phosphorus from the bones into the blood stream and causes a sharp increase in their amount in the blood and, consequently, in their elimination in the urine.

**The nervous control of renal function.** The direct influence of the nervous system on the processes of tubular reabsorption and secretion cannot be considered fully proved, although data exist in its favour. Thus, when sympathetic innervation of the kidneys is interrupted the elimination of salt increases. According to the findings of Orbeli's laboratory, stimulation of the vagus nerve leads to reduction of the salt content of urine, while its dissection has a reverse effect. It is possible that parasympathetic innervation influences tubular reabsorption.

Constriction of the renal vessels is observed when the sympathetic nerves innervating the kidneys are stimulated. The influence of vasoconstriction on urinary secretion depends on where the constriction is produced. If it occurs in the afferent glomerular arterioles, filtration pressure falls and the formation of glomerular filtrate is correspondingly reduced; but if the efferent arterioles are narrowed, then pressure in the glomeruli rises and filtration is increased.

Reflex changes in renal activity are caused by constriction or dilatation of the renal vessels and by alterations in the internal secretion of the pituitary and adrenals. That is the mechanism of pain anuria in particular, i. e. the suppression of urine formation under the stimulation of pain. As already described, pain causes the hypothalamic centres to activate secretion of the antidiuretic hormone by the pituitary gland, which leads to diminution of urinary secretion. Constriction of the renal vessels, which also reduces the excretion of urine, occurs at the same time. A reflex decrease in the flow of urine due to pain has also been encountered in a denervated kidney transplanted to the neck, but this effect is abolished by resection of the pituitary gland. On the other hand, the flow of urine from a normally innervated kidney can still be arrested by the effect of a pain stimulus even when the pituitary gland is removed. This occurs from impulses reaching the renal vessels along the sympathetic nerves. Reflex changes in urinary excretion can also be caused by stimulation of certain internal organs. Thus,

obstruction of a ureter by stone arrests urinary secretion not only in the kidney concerned but also in the other.

The control of urinary secretion, like control of the other functions of the organism, is not confined solely to the mechanisms of subcortical unconditioned reflexes. These reflexes are subordinated to higher, cortical control through the pathways of conditioned reflexes. In experiments with hypnosis marked increase of urine secretion has been observed in a subject persuaded that he had drunk much water. In experiments on dogs with a fistula of the ureter Bykov demonstrated that when the introduction of water into the stomach was repeatedly combined with the sound of a trumpet, the sound alone (without introduction of water) intensified the output of urine. The conditioned reflex was abolished by removal of the pituitary gland.

Anuria can also be caused by a conditioned reflex. If a pain stimulus is repeatedly applied to the hind legs of dogs by means of an electric current, thus causing a reflex decrease in the amount of urine passed, urine output is decreased for some time after when the animals are placed on the test stand, although no pain stimulus is applied.

Conditioned reflex influence on the kidney is effected through impulses reaching the hypothalamus and pituitary gland from the cerebral cortex, which alters the secretion of the antidiuretic hormone.

#### THE VOLUME, COMPOSITION, AND PROPERTIES OF URINE

**Volume.** The total amount of urine passed by man in a day varies widely, but averages 1.5 litres. The specific gravity of urine is between 1.012 and 1.020; its freezing point is  $-1.3^{\circ}$  to  $-2.2^{\circ}\text{C}$ . It contains about 4 per cent of solids.

With copious perspiration, at high environmental temperatures, for example, the volume of the urine passed falls owing to the loss of water in sweat.

The secretion of urine drops considerably during sleep especially when it is deep. Night urine is darker and of a higher concentration than day urine.

Secretion increases following a meal because the water and salts contained in the food are absorbed in the intestine, and there is usually a copious flow of urine of low concentration and low specific gravity.

**Composition.** The kidneys are the main route for eliminating the nitrogenous products of protein breakdown (urea, uric acid, ammonia, purine bases, creatine, and indican) from the body.

In humans and mammals urea is the main product of protein breakdown and accounts for up to 90 per cent of the total urinary nitrogen. Its concentration in urine is about 2 per cent.

Human urine usually contains 0.05 per cent of uric acid ; the daily amount does not exceed 0.5 to 1.0 gramme, but increases to two or three grammes with a diet rich in purines. The amount of uric acid decreases in the absence of purines from foods (white bread, milk, eggs, rice). The total amount of other purine compounds is about one-tenth that of uric acid.

Most of the ammonia eliminated in urine (its content is about 0.04 per cent) is formed in the kidneys themselves.

Creatine, which is formed when phosphocreatine is broken down during the contraction of muscles, is transformed into creatinine before elimination in the urine (0.075 per cent).

In addition to the nitrogenous products mentioned above, urine also contains certain derivatives of the products of protein putrefaction, i. e. indole, skatole, and phenol, formed in the intestine through the action of putrefactive bacteria. These substances are rendered harmless in the liver by the formation of conjugated compounds with sulphuric acid. They enter the urine in the form of indoxyl-sulphuric acid (indican), and skatoxyl-sulphuric, oxyphenyl-acetic, and oxyphenyl-propionic acids.

Unsplit proteins are not present in normal urine, and their appearance usually indicates a disease of the kidneys. In some cases, however, protein may be encountered in the urine of a healthy person, e. g. during strenuous muscular exercise (after long-distance races) owing to an increase in the permeability of the renal filter. The change in permeability is not pathological and disappears without trace after a rest.

Organic substances of non-protein origin also occur in the urine, namely the salts of oxalic acid, which enter the organism in food, especially with a vegetable diet, and are partly formed in the body itself; lactic acid secreted after strenuous muscular activity; acetone bodies formed in diabetes (p.380) during the conversion of fats to sugar.

Grape sugar is not present in urine if its concentration in the blood does not exceed 150 to 180 milligrams per cent. Glucose occurs in the urine only in hyperglycaemia, independently of the cause of the latter.

Besides these organic substances urine also contains pigments, which are responsible for its yellow colour. They are formed from biliary bilirubin in the intestine where it is converted to urobilin and urochrome which are partly absorbed by the intestinal wall into the blood and excreted by the kidneys. In addition, the kidneys themselves are capable of oxidizing the products of haemoglobin breakdown, transforming them into urinary pigments. Large amounts of inorganic salts (15 to 25 grammes daily) are passed in the urine, mainly sodium chloride (10 to 15 grammes), potassium chloride (3 to 3.5 grammes), sulphates (2.5 grammes), and phosphates (2.5 grammes). The last-named are responsible for the acid reaction of human urine.

The sulphates encountered in urine are formed from sulphur liberated in the breakdown of proteins; the phosphates are produced through the breakdown of lecithin, phosphorus-containing proteins, the phosphates of bone tissue, etc.

#### THE CONSEQUENCES OF REMOVAL OF KIDNEYS; AN ARTIFICIAL KIDNEY

The removal of both kidneys from animals, or acute disturbance of the secretion and elimination of urine in humans, results in uraemia, which is marked by progressive weakness, respiratory disorders, and loss of consciousness, and terminates in death in six or seven days. The main cause of this condition is the accumulation in the blood of products of protein metabolism not excreted from the organism. The blood urea content, for instance, may sometimes be as high as 900 milligrams per cent in uraemia, against a normal value in man of 30 milligrams per cent.

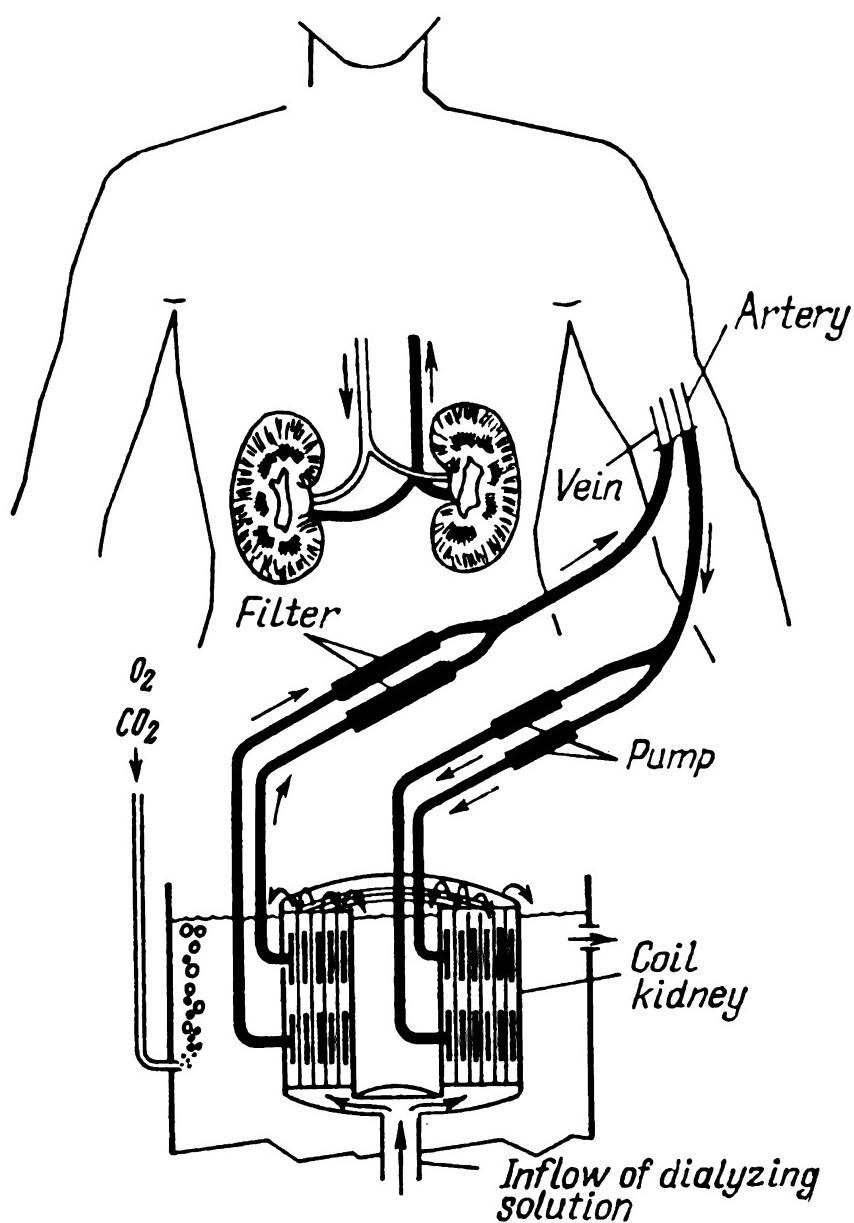


FIG. 103. Diagram of Kolf's artificial kidney connected to the patient (after Pytel)

When a kidney is removed, the remaining kidney copes adequately with the increased load, and disorders in the composition and volume of the urine do not occur.

An apparatus known as an *artificial kidney* has been used since 1943 for the dialysis of various substances from the circulation. It is used as a temporary replacement in severely disturbed renal function to remove nitrogenous substances, whose retention would poison the organism. The device consists of a thin spirally-coiled cellophane tube, which serves as a semi-permeable membrane, placed into a reservoir through which flows an isotonic saline solution heated to 37°C. The tube is connected to two cannulae, one of which is inserted into an artery and the other into a vein. As blood flows along it, a number of the substances dissolved in it diffuse through the tube into the saline solution surrounding the cellophane membrane.

There are other designs for the dialysis of the blood (haemodialysis) through a cellophane membrane (Fig. 103). With a large membrane surface 6 to 16 grammes or more of urea can be removed from the blood of an individual in an hour. The life of patients suffering from disturbances of renal function has been maintained for several years by this method. Artificial haemodialysis by means of an artificial kidney is carried out two or three times a week.

#### ELIMINATION OF URINE PASSAGE OF URINE INTO THE BLADDER

The urine produced in a kidney passes along the tubules into the renal pelvis and fills its calyces (calices renalis). As soon as the calyces are filled they contract and squeeze the urine out into the ureters, causing peristalsis of the latter. Waves of contraction occur from one to five times a minute and spread along the ureter at a rate of two or three centimetres per second. Waves are also encountered in a resected ureter placed in warmed Ringer's solution; consequently, they are caused by an automatism of the wall of the ureter itself.

The entry of urine into the bladder can be observed through a cystoscope introduced into the bladder. The instrument is supplied with an illuminating lamp and a special system of lenses and mirrors, which permit visualization of the internal wall of the bladder and the openings of the ureters. By introducing a dye into the blood that is eliminated in the urine, we can see how small portions of coloured urine are periodically discharged into the bladder during the peristaltic contractions of the ureters.

The ureters pass in an oblique direction owing to which a peculiar valve is formed where they enter the bladder and prevents regurgitation of the urine into them.

## FILLING OF THE BLADDER

The *urinary bladder* is a hollow muscular organ, which serves as a reservoir for the accumulated urine. Its evacuation occurs periodically.

At the exit from the bladder, in the urethra, there is a muscular ring forming the *sphincter of the bladder* (*sphincter vesicae*). Some distance below it lies a second sphincter, that of the urethra (*sphincter urethrae*) consisting of striated muscle. These sphincters prevent leakage of urine from the bladder. They remain constricted while the bladder is being filled; during micturition their musculature relaxes while the muscles of the bladder wall contract, which leads to emptying of the bladder.

As with other hollow organs consisting of smooth muscles, the bladder can increase in capacity during filling without any noticeable rise in the tension of its walls. This property of smooth muscle is known as *plastic tone*. Owing to it, the pressure in the bladder increases disproportionately to the amount of urine entering it. Initially there is no change of pressure, and then there is a quite abrupt rise. As soon as the volume of the urine in the human bladder reaches 250 or 300 millilitres, the tension of its muscular wall increases, its pressure rises to 15 or 16 centimetres of water, and reflex contraction may occur.

The rate of filling, i. e. the speed with which the muscular bladder wall is stretched, is the important factor. When even small amounts of urine enter quickly, the muscle of the bladder reacts to the stretching by a large increase in tension, and the intravesical pressure rises more rapidly than when it is filled more slowly with a larger volume of urine.

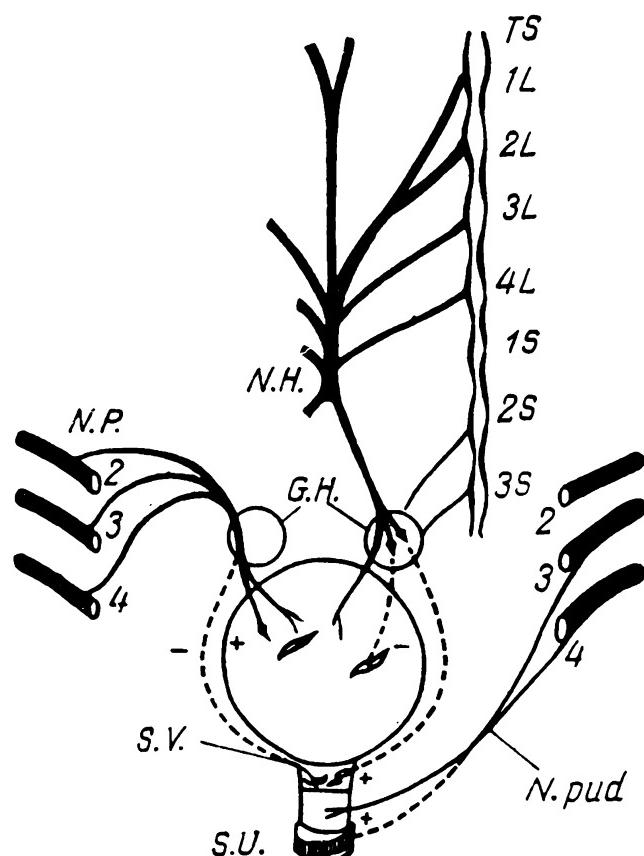
## MICTURITION

Micturition is a complex reflex act consisting in simultaneous contraction of the bladder and relaxation of the *sphincter vesicae* and *sphincter urethrae*, as a result of which the urine is expelled. Distension of the bladder and a rise in its pressure to 15 or 16 centimetres of water stimulate receptors located in its wall, and a flow of impulses is conveyed to the spinal cord along the afferent nerves. In the second, third, and fourth sacral spinal segments lies a *reflex micturition centre*, which sends impulses to the bladder along the efferent nerves. This centre is governed in turn by impulses conveyed from centres located in the medulla oblongata and the mesencephalon and in the cerebral cortex. Impulses that originate in the spinal centre cause contraction of the bladder and relaxation of its *sphincter (sphincter vesicae)*.

The apparatus responsible for the elimination of the urine has both efferent (motor) and afferent (sensory) innervation. *Efferent innervation* of the ureters and of the bladder and its sphincter is

**FIG. 104. Diagram showing the innervation of the urinary bladder and its sphincters**

N.H. — n. hypogastricus; G.H. — ganglion mesentericum inferius; N.P. — n. pelvis; N. pud. — n. pudendus; S.V. — sphincter vesicae; S.U. — sphincter urethrae; TS — truncus sympathicus. Continuous line — afferent fibres; broken line — efferent fibres. Fibres causing contraction are indicated by a plus sign, those responsible for relaxation by a minus sign



effected by sympathetic and parasympathetic nerves. The *sympathetic fibres* that supply the upper portions of the ureters arise in the plexus renalis; those that supply the lower portions of the ureters and the bladder and its sphincter originate in the ganglion mesentericum inferius.

The sympathetic impulses activate the peristaltic movements of the ureters but inhibit tonic contractions of the walls of the bladder, causing it to relax, and increase the tone of the vesical sphincter. As a consequence impulses conveyed along the sympathetic nerves create the conditions for filling of the bladder. *Parasympathetic innervation* of the urine-evacuating apparatus is effected by the pelvic nerve. The action of the parasympathetic system is the direct opposite of that of the sympathetic system. The parasympathetic nerves stimulate contraction of the vesical muscles (*m. detrusor vesicae*) and cause the sphincter vesicae to relax, that is, create conditions for emptying of the bladder.

A large number of ganglion nerve cells are distributed in the wall of the bladder and the surrounding connective tissue.

Owing to the presence of this nervous system within the organ itself, the tone of the vesical muscles is only temporarily impaired following denervation and is then partly restored.

The sphincter urethrae differs from the other muscles of the urine-eliminating tract both in structure and in function; while the vesical walls and the sphincter vesicae contain smooth muscle fibres innervated by the vegetative nervous system, the sphincter

urethrae is made up of striated fibres supplied by a somatic nerve, a branch of the pudendal nerve (Fig. 104).

Afferent nerves arising in the receptors of the ureters and bladder are included partly in the sympathetic nerves (and enter the spinal cord along the posterior roots of the lower thoracic and the upper lumbar spinal segments) and partly in the parasympathetic nerves (and pass through the posterior roots of the sacral portion of the spinal cord). The afferent pathways convey pressor and pain stimuli from the urine-eliminating apparatus to the cord. Pressor stimuli arise through distension of the bladder by urine; pain stimuli are caused by irritation of the mucous membrane of the ureters and the bladder, when, for example, stones are formed. The impulses that arise in the nerve endings of the bladder during its distension by accumulating urine enter the spinal cord and are conveyed along the afferent spinal pathways to the higher centres, in particular to the cerebral cortex. These impulses evoke a desire to micturate, and their arrival is a necessary condition for effecting cortical control over micturition.

*Cortical control* is displayed by inhibition, augmentation, or even voluntary summons of micturition.

The ability to delay micturition voluntarily develops very gradually in an infant. Some children, even of school age, can inhibit micturition only in the daytime and suffer urinary incontinence during their sleep.

## SWEATING

The glands responsible for the secretion of sweat are of importance in: 1) the elimination of breakdown products of metabolism; 2) thermoregulation, since the evaporation of sweat from the surface of the skin contributes to heat loss; 3) osmoregulation, that is, in the maintenance of a constant osmotic pressure by the elimination of water and salts.

The sweat glands are embedded in the subcutaneous cellular tissue and are distributed unevenly over the body surface, being abundant on the palms of the hands, the soles of the feet, and in the axillae, where there are 400 or 500 glands per square centimetre.

### THE VOLUME, COMPOSITION, AND PROPERTIES OF SWEAT

The sweat usually contains between 0.7 and 2 per cent of solids (0.4 to 1 per cent inorganic compounds, and 0.31 per cent organic). It also contains urea (in a concentration of 0.03 to 0.05 per cent), uric acid, ammonia, hippuric acid, indican, and non-nitrogenous organic compounds (individuals with diabetes mellitus, for example, have glucose in their sweat).

Sweat has a weak alkaline reaction; it undergoes decomposition on the surface of the body and volatile fatty acids are formed from the fats in it, owing to which it turns acid. The solids content of sweat is less than that of urine; its specific gravity varies between 1.002 and 1.003, while that of urine is usually between 1.012 and 1.020.

The volume of sweat secreted under comfortable temperature conditions averages 500 millilitres a day, and contains about two grammes of sodium chloride 0.5-1.0 gramme of nitrogen. Secretion is continuous, but as a rule sweat evaporates as soon as it reaches the skin surface.

Although sweat and urine differ in composition, the sweat glands may replace the kidneys to a certain degree when the volume of urine eliminated declines owing to renal diseases. In such cases the amount of sweat produced may be two or three times the usual volume; its composition also changes, the content of urea increasing.

#### SWEATING UNDER VARIOUS CONDITIONS

In order to observe sweating on any one part of the body or over its entire surface an attempt is usually made to cause a sharp increase in the secretion of the sweat glands.

Sweating in human beings is studied by Minor's iodine-starch method. The skin is painted with an alcohol tincture of iodine. After the alcohol has evaporated, the dry skin, slightly oiled, is covered with starch. As long as the starch remains dry the iodine has no effect upon it, but as soon as sweating begins, the starch is moistened by the sweat and is coloured blue by the iodine.

Sweating is also studied by determining the electrical resistance of the skin. This method is based on the fact that the secretion of sweat is attended with a decrease in the electrical resistance of the skin; the more the skin is moistened by sweat, the lower the resistance.

Increased sweating occurs at high environmental temperatures. A subject under test in a special chamber in which the temperature of the air is 50° or 60°C, produces 2.5 litres of sweat within 90 minutes. Sweating is also promoted by the effect of other factors that raise body temperature, for example, during strenuous muscular exertion when heat production is increased sharply owing to intensification of metabolism.

Sweating increases after a copious intake of fluid, particularly after hot beverages. A deficiency of water in the body, for instance in diarrhoea, reduces sweating. These facts are evidence of the role of the sweat glands in regulating the water balance of the organism.

Sweating is often encountered with mental excitation, and with many emotional states, e. g. anger, fear, pain. This explains the ex-

pression "to break out in a cold sweat from fear" (the sweat is called cold because it appears simultaneously with vasoconstriction which results in a cooling of the skin through decrease in the blood supply), and points to the influence of the cerebral cortex on sweating.

#### INNERVATION OF THE SWEAT GLANDS AND CONTROL OF THEIR ACTIVITY

The secretory nerves of the sweat glands are sympathetic nerves.

The sweat glands of each part of the body are innervated by a definite spinal segment. The localization of the spinal sympathetic nuclei that innervate them has been studied in subjects who have suffered injuries to various portions of the spinal cord. The centres that supply the glands of the head, neck, and upper part of the chest lie between the last cervical and sixth thoracic spinal segments; those responsible for the secretion of the glands on the upper limbs are located between the fifth and seventh thoracic spinal segments; the centres that cause sweating on the lower limbs lie in the last thoracic and upper lumbar segments.

Following injury to the sympathetic nerves sweating due to high temperature is completely suppressed on the sympathectomized (deprived of sympathetic innervation) areas of the skin. As shown in Fig. 105, Minor's test made after a unilateral resection of the cervical sympathetic ganglia reveals total cessation of sweating, or anhidrosis, on one side of the face of an individual in hot



FIG. 105. Sweating caused by high temperature after deprivation of sympathetic innervation in the left side of the face and the left hand. Minor's test (after Babsky and Lampert)

surroundings; the other side of the face, supplied with sympathetic nerves, perspires normally.

Although the nerves of the sweat glands belong anatomically to the sympathetic nervous system, their endings in the glands are cholinergic, like those of the parasympathetic nerves, that is, they liberate acetylcholine on excitation (see conduction of impulses in synapses of the vegetative nervous system, vol. II).

In man perspiring can also occur, due to emotion, after the removal of the sympathetic ganglia that innervate the sweat glands.

In addition to the spinal sweat centres there is a dominant centre in the medulla which in turn is connected with the higher vegetative metabolism centres located in the hypothalamus. And as already mentioned, there is a cortical influence on sweating.

Sweating occurs reflexly. The reflex arises from the effect of high environmental temperature, owing to excitation of the nerve endings in the skin that perceive heat (see temperature reception, vol. II). Exposure of a small area of skin to heat, a hand, for example, causes secretion not only in the sweat glands at that area but also over the entire body. This points to a spread of excitation during the sweating reflex within the limits both of the spinal segments innervating the given area of the skin and of other segments.

## SECRESSION OF SEBUM AND MILK

### THE SEBACEOUS GLANDS

A certain amount of sebum, secreted by the sebaceous glands of the skin, mixes with the sweat on the surface of the skin, making the skin softer and lubricating the hair. Sebum is fluid only when secreted, and quickly thickens. It consists mainly of neutral fats. Under the action of the acids in sweat it undergoes decomposition, producing fatty acids marked by a characteristic odour.

The sebaceous glands of the skin are located, for the most part, near the hairs, the mouths of their ducts opening into the hair follicles. They belong to the group of *holocrine glands* whose activity is associated with the destruction of the gland cells. The sebaceous glands are branching sacs covered with a membrane. The walls of the sacs are composed of stratified epithelium; as the latter grows, its cells move toward the lumen of the gland, undergo fatty degeneration, and die. The sebaceous glands are innervated by sympathetic nerves.

### THE MAMMARY GLANDS AND THE SECRETION OF MILK

The constituents of *human milk* are proteins (1.5 per cent), fats (4.5 per cent), carbohydrates (6.5 per cent), vitamins A, B, C,

and D, mineral substances (Ca, Mg, P, and others, with a total content of 0.3 per cent), and water (87 per cent). It also contains bactericidal substances and antibodies which contribute to the development of passive immunity in the child fed on it.

The *milk proteins*, casein, lactalbumin, and lactoglobulin, have all the amino acids needed by the body in the required proportions. That, plus the fact that these proteins are easily assimilated, makes milk an extremely valuable food product. It is poor in iron, however, and for that reason cannot be used as the sole source of nutrition for very long.

Milk is produced by the *mammary glands* which develop under the influence of the female sex hormone oestrogen and the growth hormone secreted by the pituitary. Maturation of the epithelium of the gland and its preparation for secretory activity occur through the action of another female sex hormone, progesterone. The great amount of oestrogen and progesterone produced by the placenta and present in the blood stream during pregnancy is responsible for the development of the mammary glands and their preparation to secrete milk. Lactation itself is induced by the influence of a lactogenic or mammotropic hormone prolactin produced by the anterior pituitary lobe (p. 403).

Oestrogens and progesterone inhibit the production of prolactin, in the absence of which lactation cannot occur. The sharp fall in the oestrogen and progesterone content of the blood after birth, caused by removal from the body of the placenta, which produces them, results in cessation of their inhibitory influence on the pituitary gland; the latter begins to synthesize prolactin in considerable quantities. The prolactin acts upon the mammary glands, which in turn begin to secrete milk.

The production of milk under the influence of prolactin is a continuous act, but it is excreted only when the child is fed. For the milk to be ejected, it must first pass from the alveoli of the gland into the ducts, which is effected by contraction of the myoepithelial cells surrounding the alveoli, an act controlled by way of a complex neuro-humoral pathway.

The sucking movements of the infant excite sensory nerve endings in the nipple. The resulting nerve impulses excite secretion in the posterior pituitary lobe by a reflex through the hypothalamus. A hormone thus liberated, *oxytocin* (p. 407), is brought to the myoepithelial cells of the gland, causing them to contract and drive milk from the alveoli into the ducts from which it is discharged.

Thus, the sucking movements made by the infant have a stimulating reflex effect on the ejection of milk; owing to activation of a humoral mechanism, however, milk does not flow immediately but only some seconds after the infant begins to suck.

The nervous system controls both the ejection of milk and its production. Tranquillity and good health in the mother promote normal lactation. Severe psychic experiences, fear, or depression cause secretion to diminish and can lead to complete suppression of lactation.

It is also known that production of milk increases under the influence of conditioned stimuli that act at the time of sucking (or when an animal is milked).

The flow of milk can continue for many months, or even several years, after parturition if the infant is not weaned.

## Chapter 9

# INTERNAL SECRETION

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### BASIC CONCEPTS

In the humoral relations of all organs, tissues, and cells there are some that play an extremely important role because substances are formed in them that are capable of causing specific changes in the metabolism, function, and structure of the others.

These substances are known as *hormones* (Gr. *horman* to excite), and the organs that secrete them as *endocrine glands* or ductless glands of internal secretion (because, unlike the glands of external secretion, they do not have ducts and discharge their secretions directly into the blood).

Hormones have a number of specific properties.

1. Each hormone acts solely upon definite organs and functions, causing specific changes.
2. They have high biological activity. One gramme of adrenaline (the adrenal hormone), for example, is sufficient to stimulate the activity of ten million isolated frog hearts; in other words, adrenaline acts on the heart in an amount of  $1 \cdot 10^{-7}$  gramme. One gramme of insulin (the hormone formed in the islets of Langerhans in the pancreas) can reduce the blood sugar level in 125,000 rabbits.
3. It is characteristic of hormones that they act at a distance; they do not influence the organs where they are formed, but act upon organs and tissues that lie some way from the endocrine glands.
4. They have relatively small molecules, which allows them to pass through the capillary endothelium separating the cells of organs and tissues from the blood stream, and through cell membranes.
5. They are

broken down rather quickly by the tissues, so that they have to be continuously secreted by the glands concerned in order to maintain an adequate amount in the blood and ensure prolonged or continuous action. 6. Most do not possess species specificity, so that hormonal preparations derived from the glands of cattle, pigs, and other animals may be used in clinical practice. Certain hormones, however, which have a protein or polypeptide structure, differ somewhat in various animal species.

Of recent years the composition of most hormones has been studied and many of them have been produced chemically in the laboratory; the stages of the synthesis of some in the organism and of their chemical transformation following entry into the circulation have been determined.

Hormones are neither enzymes nor activators of enzymes, and do not influence the course of chemical processes in a non-cellular medium. They only affect processes that occur in cells and their structures; the hormone of the thyroid gland thyroxine, for instance, influences the chemical processes in the mitochondria, increasing the intensity of oxidation in them. Insulin, the hormone secreted by the pancreas, increases the permeability of cell membranes to glucose. The antidiuretic hormone produced by the pituitary gland increases the permeability of the walls of the renal collecting tubules to water.

The production of the hormones depends upon the state of the organism and the environmental conditions. The most important factor governing its intensity is the state of the processes regulated by the hormones.

This can be regarded as a manifestation of the type of relationship known as '*feedback*'. There is two-way communication between the regulator and the regulated; the regulator not only affects the regulated process, but in turn is influenced by changes in the state of the latter.

The cells of endocrine glands liberate substances into the blood that produce changes in definite metabolic processes. Once these changes reach a certain value further production and secretion of the hormone decrease. Thus a decrease in blood-sugar content inhibits the secretion of insulin (the hormone responsible for reducing the concentration of sugar in the blood); an increase in the concentration of sodium or of calcium ions in the blood respectively inhibits the secretion of aldosterone or of the parathyroid hormone (the former brings about a raising of the concentration of sodium ions, and the latter, of calcium ions).

The secretion of hormones is regulated through a complex neurohumoral pathway. Changes in the state of physiological processes or in the level of one substance or another in the blood and tissues are perceived through special nerve endings in the organs and tissues or through special nerve cells located in the diencephalon, in the hypothalamic nuclei. These nuclei regulate metabolism in the organ-

ism and the state of the internal environment. They influence the activity of the endocrine glands by sending nerve impulses to some of them or by liberating biologically active substances that facilitate the formation of certain pituitary hormones.

The hormones secreted by the anterior pituitary lobe have the capacity to regulate the activity of other endocrine glands, the thyroid, sex glands, and adrenals.

Other parts of the central nervous system, in addition to the hypothalamic nuclei, may also influence the functioning of the adrenal glands.

Thus hormones are not independent regulators. Their formation and release into the blood are links in a single chain of neuro-humoral processes regulating the functions of the organism.

Since humoral regulation has a number of specific features of its own, study of the production and action of hormones and of disturbances in the activity of the glands of internal secretion is an independent branch of physiology known as *endocrinology*.

#### METHODS OF INVESTIGATING THE FUNCTIONS OF ENDOCRINE GLANDS

The functions of glands of internal secretion are usually studied by the following methods:

1. Observation of the results either of total or partial resection of the appropriate endocrine gland or of exposing it to the effect of certain chemical compounds, e. g. methylthiouracil (which inhibits the synthesis of thyroxine), metapyrone (which inhibits the synthesis of hydrocortisone in the adrenal cortex), alloxan (which causes degeneration of the beta-cells of the islets of Langerhans); in this way the production of definite hormones can be controlled.

2. Introduction of extracts derived from a particular gland or of chemically pure hormones into a normal animal or into an animal that has undergone resection of an endocrine gland, or had tissues of this gland transplanted into its organism.

3. Surgical union of two organisms (parabiosis) in one of which a particular gland has been damaged or removed, which permits study of the processes of compensation occurring through supply of hormones from the gland of the partner.

4. Comparison of the physiological activity of blood flowing to a gland with that of blood flowing from it.

5. Investigation of patients with deficient or excessive functioning of one gland or another, and study of the after-effects of operations performed on these patients for therapeutical purposes.

The amount of hormone present in extracts from organs and in the blood is determined by various methods, according to whether or not its chemical structure is known. If it is known, the amount is

expressed in units of weight. When it is not known the content is expressed in conventional biological units.

A *biological unit* is that amount of the preparation that has to be introduced into a definite animal in order to obtain a specific physiological effect. The greater the number of biological units contained in one gramme or one millilitre of the preparation, the higher is its activity.

### THE THYROID GLAND

The thyroid gland consists of glandular follicles filled with a semi-fluid colloid possessing high hormonal activity. The walls of the follicles are composed of glandular epithelium.

The gland is richly supplied with blood and lymphatic vessels. Between five and six litres of blood flow through the human thyroid in an hour, which corresponds to the entire volume of blood in the body, although the gland weighs only 25 or 30 grammes on average, i. e. is less than 0.05 per cent of the body's weight.

#### CHANGES IN THE STATE OF THE ORGANISM THROUGH DEFICIENT OR EXCESSIVE FUNCTIONING OF THE THYROID GLAND

Removal of the thyroid gland from young animals (young rabbits, puppies, lambs, etc.) results in retarded growth of the skeleton and a delay in development and sexual maturation. Basal metabolism drops sharply; the skin becomes rough, and the hair scanty, dry, and brittle. If the animals are fed preparations of the thyroid, treated by transplantation of the gland from another animal, or by injection of its extract, all these symptoms become less manifest or disappear.

Removal of the thyroid from tadpoles delays their development; they continue to grow but do not turn into frogs. Conversely the introduction of thyroid extracts facilitates their transition into frogs (metamorphosis), but the latter are small in size.

**Cretinism.** Deficient functioning of the thyroid gland (*hypothyroidism*) in childhood leads to the development of a disease known as *cretinism*. Its typical symptoms are retarded growth with disproportions of the body and delayed sexual maturity and mental development. A gaping mouth with the tongue constantly hanging out, and interfering with swallowing and respiration, is characteristic of the appearance; it is due to an extreme enlargement of the tongue which does not fit into the mouth. Cretinism is also attended with symptoms of myxoedema.

**Myxoedema.** Deficient functioning of the thyroid in an adult leads to the development of myxoedema, in which basal metabolism falls by 30 or 40 per cent. Body weight increases partly owing to the deposit of fat in the adipose tissue, but mainly because of an increase in the volume of tissue fluid.

The amount of mucin and albumins in the intercellular spaces of organs and tissues increases owing to impairment of protein metabolism. Proteins raise the oncotic pressure of the tissue fluid, which leads to retention of water in them, particularly in the subcutaneous cellular tissue. Mucous oedema of the tissues (myxoedema in Latin means mucous oedema) develops, attended with a slowing of thinking and speech, apathy, puffiness of the face and trunk, disturbances in sexual functions (cessation of menstruation in females), and low body temperature.

**Endemic goitre.** A high incidence of thyroid hypofunction, with marked enlargement of the gland tissue forming a goitre, is encountered in certain districts. The gland is hypertrophic and the number of follicles is increased, but total production of hormone is reduced.

The various forms of hypothyroidism, goitre in particular, are widespread in districts where the soil, and therefore drinking water and food, both of vegetable and animal origin, are poor in iodine. These districts are predominantly mountain regions, and goitre is endemic to them (an endemic disease is one constantly present in a particular district). Studies made in Switzerland and Norway show how common hypothyroidism is when the iodine content of water and food is low; more or less manifest symptoms of hypothyroidism and goitre have been encountered in more than 50 per cent of school-age children in certain mountain districts of these countries.

In the USSR endemic goitre occurs in certain regions of the Urals, Caucasus, Tien Shan, and Pamirs. Its incidence has now fallen sharply because small amounts of potassium iodine have been added to common salt or potable water in these areas.

**Hyperthyroidism.** In the sixties of the last century Basedow and Graves described a disease whose characteristic symptoms are enlargement of the thyroid gland (basedowian goitre); exophthalmos (protrusion of the eyeballs), acceleration of the heart beat, extreme nervous excitability, heightened basal metabolism and body temperature; and although the individual eats much food wasting occurs (Fig. 106).

Basedow's (Graves') disease results from hyperthyroidism, i. e. excessive production of the thyroid hormones with their content in the blood raised to a concentration that has toxic effects. For that reason it is also known as *thyrotoxicosis*.

With slight hyperthyroidism a number of symptoms characteristic of Basedow's disease are absent; there is no protrusion of the eyeballs, no extreme wasting, no sharply displayed nervous excitability, and a goitre cannot be seen or even palpated. In these cases the hyperthyroidism is displayed by an increase in basal metabolism, a rise of energy expenditure during work compared with a healthy individual, a slow return of the metabolic rate to its value at rest, accelerated heart beat, and an increase in the blood iodine content. Tendon reflexes are hyperactive and tremor of the muscles may be



**FIG. 106. Patient with Basedow's disease  
Left, before the operation; right, soon after the operation (after Shereshevsky)**

encountered. These patients are noted for their lively temperament, restlessness, and occasional unrestrained behaviour.

#### HORMONES OF THE THYROID GLAND AND THEIR PHYSIOLOGICAL SIGNIFICANCE

Thyroid tissue contains iodine, which is a constituent of the hormones secreted by the gland. If radio-active iodine ( $I^{131}$ ) is introduced into an animal, part of it is eliminated in the urine through the kidneys, another part enters the saliva, gastric juice, and bile, but most of it settles in the thyroid gland. A characteristic of its cells is their ability to accumulate iodine so that its concentration in them becomes three hundred times that in the blood plasma. When there is a deficiency of the iodine required to synthesize the thyroid hormones the gland tissue proliferates and a goitre is formed.

The iodine, accumulated by the thyroid cells, is utilized to synthesize a number of iodized compounds, mono-iodotyrosine, di-iodotyrosine, tri-iodothyronine, and tetra-iodothyronine (thyroxine). In the cells of the follicles these form a complex compound with protein, thyroglobulin, which may be stored in the follicles for several months. When it is hydrolysed by proteinase formed in the gland cells active hormones, *tri-iodothyronine* and *tetra-iodothyronine*, or *thyroxine*, are liberated, which pass into the blood where they combine with the plasma alpha-globulins, carriers of these hormones. When the content of thyroxine or tri-iodothyronine in the blood

is raised they may also combine with plasma albumins. These complexes are broken down in the tissues, liberating thyroxine and tri-iodothyronine.

The characteristic effect of the thyroid hormones, intensification of energy metabolism, does not begin immediately that thyroxine is introduced, but only after 24 hours, and reaches its maximum twelve days later. With tri-iodothyronine the increase in energy metabolism begins earlier, six to twelve hours after its introduction; but if another compound, *tri-iodothyroacetic acid*, is injected the rise in metabolism begins immediately. For that reason it is assumed that the active principle affecting metabolism is tri-iodothyroacetic acid, which is formed more quickly in the tissues from tri-iodothyronine than from thyroxine.

**The action of the thyroid hormones.** Thyroxine, tri-iodothyronine, tri-iodothyroacetic acid, and certain other iodized compounds formed in the thyroid gland, cause a sharp augmentation of oxidative and proteolytic processes. The oxidative processes in the mitochondria are most activated, which leads to an intensification of cell energy metabolism.

Administration of thyroxine or tri-iodothyronine causes a considerable increase in the basal metabolism of animals. The introduction of one milligram of thyroxine increases daily energy expenditure in man by about 1,000 kilocalories. The intensification of oxidation is naturally followed by an increase in the consumption of oxygen and elimination of carbon dioxide; the organism becomes extremely sensitive to oxygen deficiency, and tolerates high altitudes with difficulty.

Along with the rise in basal metabolism, there is also an increase of energy expenditure on the performance of external work. With a normally functioning thyroid gland working allowances for metabolism average 1.2 kilocalories per kilogram-metre of work performed; but with very pronounced hyperfunction of the thyroid gland it may be as high as 2.8 kilocalories. Thus, overactivity of the gland leads to a sharp increase of heat production during muscular effort.

Thyroxine promotes expenditure of all types of nutrients — carbohydrates, fats, and proteins, and intensifies the consumption of blood glucose by the tissues. The glucose lost by the blood is compensated through intensified breakdown of glycogen in the liver and muscles. The intensified expenditure of fats resulting from daily administration of thyroxine over a long period of time leads to a reduction of the respiratory quotient to 0.75, i. e. brings its value close to that characteristic of fat oxidation. In such cases only a third of the normal amount of fat is retained in the muscles and one-half in the liver. The heightened expenditure of proteins caused by the introduction of thyroxine leads to an increase in urinary nitrogen. Deamination of amino acids in the liver is increased in animals given thyroxine.

Thyroxine not only raises energy metabolism, but also anabolism which is manifested in a more rapid development.

The thyroid hormones have a stimulating effect on the central nervous system. Dogs given thyroxine in large doses for many days become restless, and often shudder; the tendon reflexes (knee jerk, for example) are hyperactive; tremor of the legs is encountered, particularly when the leg is stretched and dangles. Similar phenomena are encountered in man with overactivity of the thyroid gland.

According to Valkov's research the production of conditioned reflexes in dogs deprived of the thyroid gland is extremely difficult; a conditioned reflex induced within one day proves to be exhausted on the next day and has to be elaborated again. It has been shown that the thyroid hormones not only act upon the cerebral cortex directly, but also influence it through the reticular formation of the brain stem (see Reticular Formation of the Brain Stem, vol.II). They accumulate in the structures of the latter in greater amounts than in the other parts of the central nervous system, and by increasing its tone have an activating effect on the cortex.

#### CONTROL OF THYROID FUNCTIONS

The thyroid gland is richly supplied with afferent and efferent nerves. Impulses reaching it along the sympathetic nerve fibres stimulate its activity. This has been proved in experiments on cats by suturing the central segment of the phrenic nerve to the peripheral end of the cervical sympathetic nerve, the branches of which innervate the thyroid gland. Some time after the operation the phrenic nerve grows into the gland and rhythmic impulses from the respiratory centre are conveyed to the cells along its fibres. As a result of the continuous arrival of impulses the secretion of the gland cells is intensified and liberation of the thyroid hormone increased. This causes a condition of hyperthyroidism in the animal; its basal metabolism increases, body weight is lost, and the heart beat is accelerated.

Experiments on dogs have also shown that electrical stimulation of certain parts of the reticular formation through implanted electrodes alters the intensity with which the thyroid gland absorbs inorganic iodine from the blood and the intensity with which the hormones are released into the blood.

Reflex control brings about an augmentation of thyroid activity in response to cold, which, by increasing metabolism, facilitates acclimatization. The influence of the higher parts of the central nervous system on the gland is proved by the fact that mental emotions, happy, and especially, distressing events, and difficult problems cause a sharp aggravation of the disease in persons suffering from hyperfunction and increase reflex stimulation of the already augmented thyroid activity.

Thyroid function is controlled by a thyrotropic hormone secreted by the anterior pituitary lobe. This hormone stimulates the breakdown of thyroglobulin and the release of the hormones stored in the gland, facilitates passage of iodine into the cells and hormone synthesis, and causes an increase in the number and size of the gland cells.

Secretion of the pituitary thyrotropic hormone is controlled by the hypothalamic nuclei, and depends upon the amount of thyroxine and tri-iodothyronine circulating in the blood. Introduction of thyroxine into the blood inhibits secretion of the hormone, but this reaction is not encountered if the hypothalamus has been destroyed. Thus the hormonal regulation of thyroid activity is also under nervous control. It follows that the nervous system controls the work of the thyroid gland in two ways: a) by sending impulses directly along the sympathetic nerves that innervate it and b) by stimulating secretion of the pituitary thyrotropic hormone. It is supposed that thyroid hyperfunction is caused by excessive secretion of this hormone by the anterior lobe of the pituitary. The mechanisms underlying the development of chronic hyperthyroidism have not yet been sufficiently studied, but clinical observations indicate that severe mental anxiety often contributes to occurrence of the condition; a severe case has been described that developed very rapidly in a woman after her two children had died almost simultaneously from an infectious disease.

Synthesis of the thyroid hormones is suppressed in hyperthyroidism by the use of preparations (derivatives of thiourea like methythiouracil and others) which have a specific effect on the thyroid cells concerned with secretion, inhibiting their production of hormones.

#### THE PARATHYROID GLANDS

There are four parathyroid glands in man, two on the posterior surface of the thyroid gland, and two others on its lower portion or sometimes actually embedded in its tissue. They are slightly flattened oval bodies 6 or 7 mm long, 3 or 4 mm wide, and 1.5 to 2 mm thick. Their tissue is richly supplied with blood and lymphatic vessels and they are innervated through the superior laryngeal nerve.

#### CHANGES RESULTING FROM MALFUNCTIONING OF THE PARATHYROID GLANDS

The consequences of abolished parathyroid activity have been studied in experiments on parathyroidectomized dogs. A few days after the operation spasms of all the skeletal muscles, gradually increasing in intensity and frequency, are encountered, and so-called *parathyroprival tetany* develops.

Lack of the parathyroid glands finally results in death, the immediate cause of which is disturbance of respiration due to spasms of the respiratory muscles. The spasmodic attacks are caused by disorders in the central nervous system and not by disturbances in the skeletal muscles, as is indicated by the fact that spasms do not occur in muscles when the motor nerves supplying them are cut.

Parathyroprival tetany develops as a result of a reduction in blood calcium level. Its prevention in parathyroidectomized dogs by the administration of calcium salts is proof of this. Tetany is also attended with disturbances in the synthesizing functions of the liver; ammonium carbamate, which is toxic, is encountered in the blood.

Deficiency in the internal secretion of the parathyroids, or *hypoparathyroidism*, in man may be either acquired or congenital. Owing to the decrease in blood calcium level the excitability of the central nervous system is greatly heightened in this condition, which causes attacks of tetanic spasms.

Both acute and latent forms of tetany have been described. With latent tetany, which occurs with mild dysfunction of the parathyroid glands, spasms of the muscles of the face or hand appear only when pressure is applied to the nerve supplying them.

In children with a congenital parathyroid deficiency the growth of bones, teeth, and hair is impaired, and protracted spasms of groups of muscles (of the forearm, chest, pharynx, etc.) occur. The amount of calcium in the blood of the patients is reduced.

Overactive secretion (hyperfunction) of the parathyroid glands is a rare disease encountered with a malignant tumour of the gland. In it the calcium content of the blood is increased, while the content of inorganic phosphorus is reduced. No other characteristic symptoms appear for a long time; then osteoporosis, i. e. destruction of bone tissue, becomes visible on X-rays. A progressive weakness of the muscles forces the patient to take to his bed, and pains in the back, legs, and arms appear. Timely surgical removal of the tumour affecting the parathyroid gland considerably improves calcium and phosphorus metabolism, relieves the pain, and restores a more or less normal condition.

#### PHYSIOLOGICAL IMPORTANCE OF THE PARATHYROID HORMONE

The disorders that occur in the organism with dysfunction of the parathyroids depend upon the changes in blood calcium ion content. Lack of the hormone secreted by these glands (called parathormone) reduces, and excess increases, blood calcium content. Parathormone is a protein or a large polypeptide that is broken down under the action of trypsin, or on being brought to the boil with acids or alkalies. Preparations of it break down in the alimentary

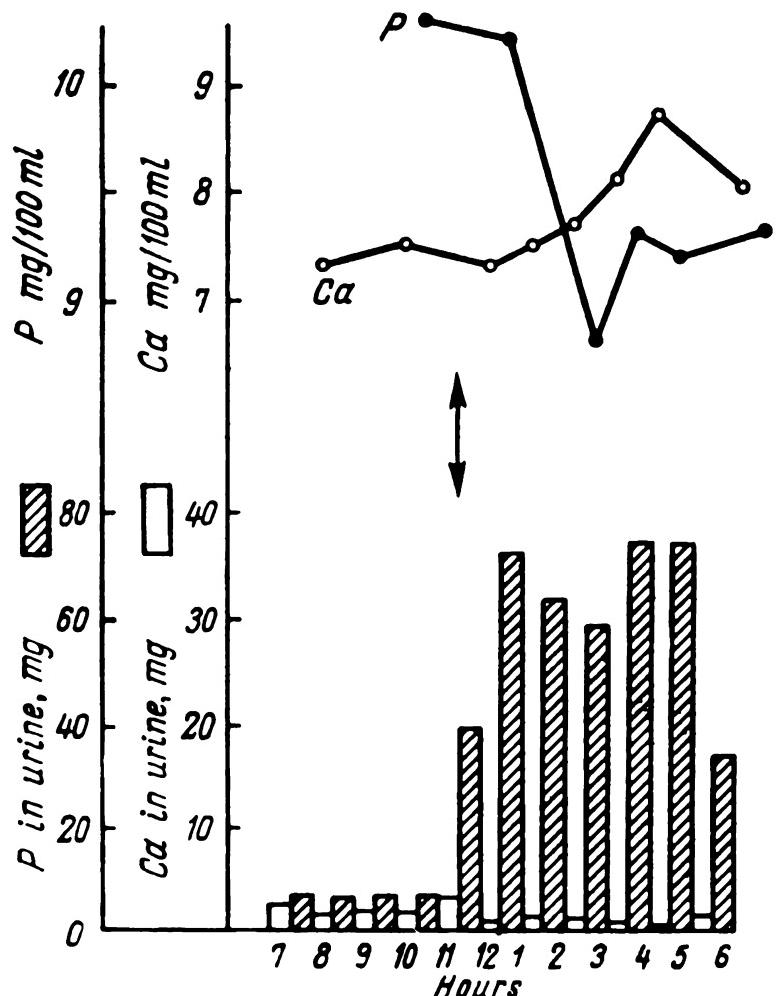


FIG. 107. Effect of an injection of 75 units of parathyroid hormone on serum calcium and phosphorus levels (top) and urinary calcium and phosphorus excretion (bottom) in a patient with deficient parathyroid activity (after Albright)

The arrow indicates when the hormone was injected

tract if given with food, and therefore have to be injected subcutaneously. Its exact composition and chemical structure are not known.

The parathyroid hormone has a specific action of activating the osteoclasts, which destroy bone tissue. It produces this effect not only in the organism, but also in cultures of isolated bone tissue; addition of the hormone to the culture sharply increases the activity and number of the osteoclasts in it.

In the organism parathormone causes the destruction of bone tissue and the liberation of calcium ions, owing to which their concentration in the blood increases. It also activates other processes responsible for a rise in blood calcium level; it promotes the absorption of calcium in the intestine and its reabsorption in the renal tubules. All this leads to a considerable increase in the level of calcium in the blood (to 18 milligrams per cent and higher against a normal level of 10 or 11 milligrams per cent). The level of phosphorus in the blood falls simultaneously, because parathormone stimulates elimination of phosphorus in the urine (Fig. 107).

With a deficient supply of the parathormone in the blood, the concentration of calcium in the plasma may drop to 5 milligrams per cent.

## CONTROL OF PARATHYROID FUNCTION

The concentration of calcium in blood plasma is usually very accurately maintained and rarely deviates by more than 0.5 milligram per cent above or below the normal level in a healthy individual; it is, indeed, of the most precisely regulated factors of the internal medium.

The narrow limits of blood calcium variation are due to the fact that the secretion of parathormone into the blood is controlled. A drop in blood calcium level leads to intensification of endocrine secretion in the parathyroids, accompanied with liberation of an increased amount of calcium from the bone depots into the blood. Contrariwise, an increase in the amount of this electrolyte in the blood inhibits secretion of parathormone which results in a reduced calcium level. Thus, there is a two-way connection between parathyroid activity and blood calcium content.

Several investigators suggest that the activity of parathyroid cells may be directly dependent upon the concentration of calcium ions in the blood flowing through the glands, an increase automatically inhibiting secretion of parathormone.

## THE PANCREAS

Histological studies of the pancreas have shown that it contains, as well as the secretory epithelium that produces digestive juice, a peculiar group of cells called the *islands* or *islets of Langerhans* after the scientist who discovered them. These islets have no excretory ducts and discharge their secretion directly into the blood.

### CHANGES RESULTING FROM DISTURBANCES OF PANCREATIC SECRETION

As early as 1889 Mering and Minkowski demonstrated that removal of the pancreas from a dog was followed in four or five hours by elimination of sugar in the urine. There was also a marked increase in blood glucose. The loss of sugar in the urine resulted in wasting of the animal, it drank much water and had a voracious appetite.

All these symptoms proved to be analogous to those encountered in humans with the disease known as sugar diabetes, or diabetes mellitus. Proof that this condition was due to deficient internal secretion of the pancreas was provided by Minkowski who demonstrated that diabetes that had already set in was arrested by transplantation of the pancreas into any part of the animal's body, for instance, under the skin.

The principal manifestation of diabetes mellitus is an increase in the blood-glucose content (*hyperglycaemia*) which may be as high

as 200 milligrams per cent or more instead of the normal 100 to 120 milligrams per cent. A particularly sharp increase occurs following a meal rich in carbohydrates, because in diabetes not all the glucose that passes into the blood is utilized by the tissues and converted to glycogen.

An increase in the glucose level of the blood, and consequently of the glomerular filtrate, results in its incomplete reabsorption by the epithelium of the renal tubules, owing to which it is discharged in the urine (glycosuria). This loss of sugar in the urine caused the condition to be called *diabetes mellitus* (Gr. *diabetes* to pass through, *meli* honey.)

With diabetes there is an increase in the quantity of urine (*polyuria*) because the high glucose content of the fluid in the renal tubules produces a high osmotic pressure and retains water. The reabsorption of water by the tubules becomes insufficient and the volume of urine eliminated by the kidneys increases. The loss of water by the organism causes a sensation of thirst in diabetic patients and forces them to drink excess amounts of water (*polydipsia*). The utilization of carbohydrates for energy needs is limited, so that the expenditure of proteins and fats to provide energy metabolism in the body is sharply increased. A decline in the respiratory quotient (not infrequently down to 0.7) is evidence that the combustion of fats and proteins in the body has increased.

Products of incomplete oxidation of fats accumulate in the organism including the ketones: beta-oxybutyric and aceto-acetic acids.

In severe cases the intensified formation of acid products of fat breakdown and deamination of amino acids in the liver cause a shift in the active reaction of the blood towards acid, *acidosis* (p. 59). Acidosis leads (due to the binding of the alkaline metals of blood plasma by the products of incomplete oxidation of fats and amino acids) to a decrease in the alkali reserve, compensatory dyspnoea, and a shift of the urine reaction towards acid.

Considerable acidosis in a diabetic patient can give rise to a severe condition that may prove fatal—*diabetic coma* marked by respiratory disturbances and loss of consciousness.

The disorders described are associated with deficient production of one of the hormones secreted by the pancreas *insulin*.

#### PANCREATIC HORMONES

The islets of Langerhans consist of three types of cell—alpha, beta, and gamma.

The beta-cells are the most numerous (about 75 per cent in dogs). They are small, have a granular protoplasm, and secrete the hormone *insulin* (L. *insula* island). Alloxan injected into an animal causes the death of these cells and, as a consequence, arrest of insulin secretion and the development of diabetes.

The alpha-cells of the islands produce the hormone *glucagon*. Cobalt salts introduced in large doses cause the death of alpha-cells in animals and inhibit production of glucagon.

It has been suggested that the epithelium of the small pancreatic ducts secretes the hormone *lipocaine*.

Two other hormones, *vagotonin* and *centropnein*, have been found in pancreatic extracts.

**Insulin.** Attempts to extract insulin from the pancreas proved futile for a long time because it is a protein and is digested by the pancreatic juice in the removed and minced pancreas. In 1902 Sobolev proposed two methods that would prevent digestion of the insulin. One was as follows: a few days before the pancreas was removed, its ducts were ligated so that the epithelium concerned with external secretion degenerated and died. As a result, the pancreas contained no juice that could cause enzymic splitting of the insulin. The other method involved extraction of the hormone from the pancreas of embryos in which digestive juice had not yet formed. In 1922 Banting and Best obtained active preparations of insulin by the first method.

The chemical structure of insulin has since been determined. It proved to be a polypeptide consisting of two chains of seventeen different amino acids linked by disulphide bridges (one chain consists of 21 amino acids and the other of 30). Insulin preparations, though as yet weakly active, have been synthesized, and are, in fact, the first protein obtained synthetically outside the organism. The insulins derived from the pancreas of various animals differ in the position of the amino acids in their molecules. The insulin molecule does not contain zinc, but can combine with it, which lengthens and intensifies the effect produced by the insulin.

Insulin increases the permeability of cell membranes to glucose and greatly accelerates the passage of glucose into cells from the intercellular fluid. In a medium free of insulin the rate at which glucose penetrates the cell is only 5 per cent of that in a medium with an adequate insulin content. Since the enzyme reactions governing utilization of glucose, both its phosphorylation and its oxidation, and the formation of glycogen take place in the cell, insulin, by facilitating transport of glucose into the cell, ensures the performance of all aspects of its utilization. At the same time, it has no effect on the utilization of carbohydrates by non-cellular homogenates of the tissues (homogenates are prepared by finely mincing cells so that the cell membranes are destroyed). This is evidence that the mechanism underlying the influence of insulin on carbohydrate metabolism is associated with an intact cell structure and with its effect on the permeability of the cell membrane.

The increase in the passage of glucose across the membranes of muscle fibres and hepatic cells through the action of insulin facilitates synthesis of glycogen and its accumulation in the cells of the

liver and muscles. By raising glucose utilization, insulin stimulates the formation of fat in the body. The passage of considerable amounts of glucose from the blood plasma into the cells of the skeletal, cardiac, and smooth muscles, and into the cells of the mammary glands, liver, and certain other organs, following the introduction of large doses of insulin, causes a drop in the blood-glucose level and a resultant deficiency of glucose in the cells of the nervous system, whose permeability is not influenced by the hormone. Consequently the brain and the spinal cord suffer an acute lack of glucose which is the main energy source for the activity of all cells, nerve cells included. As a result, the sharp reduction of blood glucose causes acute disturbances in cerebral activity, *insulin*, or *hypoglycaemic shock*. The condition occurs as soon as blood sugar drops to 45 to 50 milligrams per cent, and is marked by periodic attacks of severe contractions followed by a drop in muscle tone, low body temperature, and loss of consciousness. Hypoglycaemic shock can even be caused by a small dose of insulin if it is injected on a fasting stomach when no glucose is entering the blood from the alimentary tract. An intravenous injection of glucose solution relieves the shock immediately.

**Glucagon**, the second pancreatic hormone, is secreted by the alpha-cells of the islets of Langerhans and is a polypeptide of relatively low molecular weight (about 3,500). Chemical research has revealed its structure. Glucagon promotes the intracellular conversion of inactive phosphorylase (an enzyme concerned in the breakdown of glycogen and formation of glucose) to an active form, and thus brings about a sharp increase in the blood-sugar level. It is an antagonist of insulin in this respect, since the latter causes a reduction of blood-sugar level. The use of glucagon for therapeutical purposes, however, is limited, because it is rapidly broken down in the blood.

**Lipocaic** is a polypeptide apparently formed in the epithelial cells of the excretory ducts of the pancreas. Its chemical structure is not known. The hormone is not destroyed by the enzymes in the digestive juices and for that reason affects the organism even if given by the mouth. Lipocaic stimulates the production of phospholipids (lecithin) and the oxidation of fatty acids in the liver, i.e. facilitates the utilization of fats. It prevents fatty degeneration of the liver in depancreatized dogs (carbohydrate metabolism is controlled in such animals by subcutaneous injections of insulin).

**Vagotonin** is a protein whose composition has not yet been determined. Its introduction into the body raises the tone of the vagal nuclei and stimulates the activity of the parasympathetic nervous system. It also stimulates the blood-formation processes, in particular the formation of erythrocytes.

**Centropnein** is another protein of unknown composition. It stimulates the respiratory centre and causes dilatation of the bronchi;

therefore its administration for the spasms of the bronchial muscles encountered in bronchial asthma improves the patient's condition.

In addition centropnein facilitates the uptake of oxygen by haemoglobin and promotes its carriage. Hence it increases the resistance of the organism to oxygen lack, to a certain extent.

#### CONTROL OF PANCREATIC SECRETION

Insulin is produced continuously in the islets of Langerhans but its volume increases during digestion and decreases during fasting. The rise in insulin secretion during digestion promotes intensified production of glycogen in the liver and muscles from the glucose then passing into the blood from the intestine.

Secretion of insulin is controlled by the nervous system through the vagus and sympathetic nerves. Excitation of the vagus nerve stimulates its secretion, while sympathetic stimulation inhibits it.

Insulin secretion is increased by reflex during digestion as a result of impulses reaching the pancreas from nuclei of the vagus nerves.

The rise in blood sugar level that occurs following a large intake of glucose, or in the hyperglycaemia associated with strenuous physical work and emotions, raises insulin secretion. On the contrary, a decrease in the blood-glucose level inhibits the secretion of insulin and stimulates secretion of glucagon. Thus, the intensity of insulin and, apparently, of glucagon secretion depends upon the level of glucose in the blood. Therefore hormones that do not act directly upon the pancreas can stimulate insulin secretion by changing carbohydrate metabolism; these hormones include adrenaline, secreted by the adrenal medulla, which stimulates the formation of glucose from glycogen (p.384); the glucocorticoids, secreted by the adrenal cortex, which stimulate the formation of glucose from amino acids (p.389), and thyroxine which raises energy expenditure and breakdown of glucose.

#### THE ADRENALS

The adrenals or suprarenal glands consist of two parts, the medulla and the cortex, which are glands of internal secretion differing from each other both in structure and function and in the hormones they secrete, which have quite different actions.

##### THE ADRENAL MEDULLA

The adrenal medulla is composed of cells embryogenically related to the cells of the sympathetic nervous system. They stain yellow-brown with potassium bichromate and for that reason are called chromaffin cells.

Chromaffin cells not only occur in the adrenal medulla, but are also encountered in other parts of the body, namely, along the aorta, at the site of the carotid bifurcation, among the cells of the sympathetic ganglia located in the small pelvis, and sometimes in the mass of separate ganglia of the sympathetic chain. They all belong to the so-called adrenal system because they produce physiologically active substances similar to adrenaline.

**Changes occurring in the organism with disturbed secretion by chromaffin tissue.** When the chromaffin tissue of both adrenals is removed (it is imperative that the cortex be left in place), animals display a lower resistance to severe conditions of existence; for example, such animals die more often of traumatic shock due to injuries than animals with intact adrenals. Among the various human endocrine diseases there are none that are directly caused by deficient function of the chromaffin tissue of the adrenal medulla. That may depend on the fact that chromaffin tissue is found in other parts of the organism, apart from the adrenals, and on the fact that the substances produced by the adrenal medulla are also secreted by the endings of sympathetic nerve fibres.

Hyperfunction of the adrenal chromaffin tissue is encountered in people suffering from tumours of this tissue (chromaffin-cell paragangliomas or pheochromocytomas). They display paroxysmal hypertension, i. e. a sudden temporary elevation of arterial pressure to a very high level (200 millimetres mercury or higher), attended by pallor, tremor of the muscles, dilatation of the pupils, accelerated heart beat, vomiting, and giddiness.

#### PHYSIOLOGICAL SIGNIFICANCE OF ADRENALINE

Adrenaline (or epinephrine), the hormone secreted by the adrenal medulla, is a derivative of tyramine which in turn is a product of the decarboxylation of tyrosine in the kidneys. The immediate precursor of adrenaline in its synthesis in the adrenals is noradrenaline, dimethylated adrenaline, which has a similar action.

Adrenaline and noradrenaline are referred to together as *catecholamines* because they are derivatives of catechol. They are also called *sympathomimetic amines* because their effect on the organs and tissues is similar to that of the sympathetic nerves. Sympathomimetic amines are broken down in the blood and tissues by the enzyme amine oxidase; the various oxidation products of adrenaline formed have been studied by Utevsky; though similar in structure to adrenaline, they do not possess its characteristic action.

Adrenaline influences many functions, including intracellular metabolism. It promotes the breakdown of glycogen, for example, and reduces its reserves in the muscles and liver, in this respect being an antagonist of insulin which increases glycogen synthesis.

Glycogenolysis is intensified in the muscles under the effect of adrenaline along with glycolysis and the oxidation of pyruvic and lactic acids. In the liver glucose is formed from glycogen, and then passes into the blood; in consequence there is a rise in the blood-glucose content (adrenaline hyperglycaemia). Thus the effect of adrenaline brings about first a using up of the glycogen reserve in the muscles, as a source of energy for their work, and second, an increased supply of glucose in the blood from the liver which can also be used for work by the muscles.

Adrenaline intensifies and accelerates cardiac contraction, and improves the conduction of the excitation in the heart. It has a particularly marked effect on weakened cardiac muscle. The hormone constricts the arterioles of the skin, the abdominal organs, and skeletal muscles that are at rest. It does not, however, affect the vessels of working muscles because the metabolites formed in them are vasodilative. As a result of the intensified cardiac contraction and the constriction of arterioles, arterial pressure rises.

Adrenaline inhibits contraction of the stomach and small intestine; the peristaltic and pendulum contractions diminish or even cease completely. The tone of the gastric and intestinal smooth muscles falls. The bronchial muscles relax, and the lumina of the bronchi and bronchioles expand as a result. In certain other organs the smooth muscles contract under the action of adrenaline; for instance, the radial muscle of the iris contracts with a resultant dilation of the pupils. Contraction of the smooth muscles of the skin that raise the hair (pilomotors) produces "goose flesh" and a raising of the hair.

Injection of adrenaline raises the working capacity of skeletal muscles, especially those that are tired. The excitability of receptors is increased by adrenaline, particularly those located in the retina, the ears, and the vestibular apparatus, which promotes perception of external stimuli by the organism.

Thus, adrenaline can bring about an urgent reorganization of functions in order to raise the working capacity of the organism in exceptional circumstances.

The effect of noradrenaline which has been studied in detail by Euler, is similar to that of adrenaline but not quite the same, and on certain functions may even be the opposite. Thus adrenaline accelerates the rhythm of cardiac contraction in humans and relaxes the pregnant uterus, while noradrenaline slows down the rate of cardiac performance and stimulates contraction of the uterus.

#### NERVOUS CONTROL OF CHROMAFFIN SECRETION IN THE ADRENALS

In 1910 Cheboksarov demonstrated that stimulation of the fibres of the splanchnic nerve innervating the adrenals caused an increased

secretion of adrenaline, while severing of this nerve led to a decrease. It follows from that that hormone production by the chromaffin tissue is controlled by the nervous system through the sympathetic nerve fibres that are part of the splanchnic nerve.

The nerve centre controlling the secretory activity of the chromaffin tissue of the adrenals is located in the hypothalamus where the higher vegetative centres lie. Experimental stimulation of the hypothalamus results in an increase in the catecholamine content of the blood.

The secretion of both adrenaline and noradrenaline by the adrenals is increased by stimulation of their secretory nerves. At first much more adrenaline is produced, but as stimulation continues the ratio changes in the direction of a reduced adrenaline flow and a rise in noradrenaline. With prolonged stimulation of their activity, the adrenals synthesize less hormone to the stage of adrenaline and secrete more of its precursor, the intermediate product noradrenaline.

With all conditions associated with intensified activity of the organism and intensified metabolism, for example emotional excitation, muscular work, cooling of the body, etc., the secretion of adrenaline by the adrenals increases.

The intensified secretion of adrenaline with emotional excitation was established by Cannon, who observed a rise of its adrenaline content in the suprarenal veins of a cat at the sight of a barking dog.

The increased secretion explains the mechanism underlying a number of the physiological changes in emotional states. For instance, the rise in the level of glucose in the blood and its elimination in urine encountered in students taking examinations and in athletes waiting at the start of races is due to increased discharge of adrenaline by the adrenals; and this is evidence that cerebral centres exert an influence on its secretion.

Secretion of adrenaline is stimulated by a decrease in blood glucose; when hypoglycaemia is induced in an animal with insulin, for example, it is followed by intensified secretion of adrenaline, which brings about a mobilization of glycogen from the liver, so that the level of blood glucose rises.

#### THE ADRENAL CORTEX

The cells of the adrenal cortex are genetically related to the epithelial cells. They form three zones, an external glomerular zone (*zona glomerulosa*), a middle fascicular zone (*zona fasciculata*), and an internal reticular zone (*zona reticularis*). More than forty corticosteroids have been derived from the adrenal cortex, but only eight are physiologically active.

**Changes arising from dysfunction of the adrenal cortex.** An animal dies quickly after the removal of the adrenal cortex, and it has shown that death is mainly due to copious loss of sodium

in the urine and the resultant sharp drop in sodium levels in the blood and tissues. The life of decorticated animals can be prolonged for some time by introducing large amounts of sodium.

A sharply deficient production of hormones by the adrenal cortex is encountered in the grave disease described in 1855 by Addison, and known as *Addison's disease* (or bronzed disease). Its early symptoms are bronzing of the skin especially on the hands, neck, and face (hence the name bronzed disease); weakness of the cardiac muscle; asthenia (increased fatigability during muscular effort and mental work). The condition is marked by lack of appetite, nausea, vomiting, diarrhoea, and low acidity of the gastric juice. The patient is sensitive to the cold and to pain stimuli, and very susceptible to infection, loses considerable weight, and gradually becomes completely emaciated. The disease is very often fatal. Preparations of the adrenal cortex bring some relief and help to maintain a certain degree of working capacity.

Sharply pronounced hyperfunction of the adrenal cortex is relatively rare and develops with an adrenal tumour or hypernephroma. The hormone-producing activity of the adrenal cortex not only increases, but changes in character; two sex hormones are secreted, male and female, which are normally only formed in small amounts in the adrenal cortex. Hence more or less pronounced changes in sexual development occur in patients with hypernephroma. Cases have been described of premature puberty, growth of a beard, and growth of hair at the pubis in three and four-year old boys. Cases of hypernephroma in women with cessation of menstruation and the appearance of a beard and a hoarse male voice are also known. The disorders are eliminated by removal of the tumour.

#### HORMONES OF THE ADRENAL CORTEX

The cortical hormones may be divided into three groups:

I. *Mineralocorticoids* — *aldosterone*, *corticosterone*, and *deoxycorticosterone* — secreted by the glomerular zone and regulating mineral metabolism.

II. *Glucocorticoids* — *cortisone*, *hydrocortisone*, and *corticosterone* (the latter is a mineralocorticoid at the same time) — secreted by the fascicular zone, and influencing the metabolism of carbohydrates, proteins, and fats.

III. *Sex hormones* — *androgens*, *oestrogens*, and *progesterone* — secreted by the reticular zone.

**Mineralocorticoids** control mineral metabolism in the organism, primarily the sodium and potassium levels of blood plasma.

*Aldosterone* is the most active of this group. It facilitates reabsorption of sodium and chloride in the renal tubules, which raises the sodium chloride content of the blood, lymph, and tissue fluid. At the same time it reduces reabsorption of potassium in the renal

tubules which intensifies loss of potassium and lowers its level in the organism.

The increased concentration of sodium chloride in the blood and tissue fluid due to aldosterone causes a rise in their osmotic pressure, leads to retention of water in the organism and contributes to an increase in arterial pressure. Intensified sodium reabsorption can give rise to alkalosis.

A deficiency of mineralocorticoids has an opposite tendency. Reabsorption of sodium in the renal tubules decreases and the organism suffers such a loss of the mineral that changes incompatible with life take place in the internal environment and death occurs a few days after removal of the adrenal cortex. The life of an adrenalectomized animal can only be maintained by introducing large amounts of sodium or mineralocorticoids. For that reason mineralocorticoids are known as "life saving hormones".

**Control of mineralocorticoid level.** Secretion of mineralocorticoids by the adrenals is directly dependent upon the level of sodium and potassium in the organism. An increase in the amount of sodium, through injection, for example, inhibits aldosterone secretion, which leads to intensified elimination of sodium in the urine. A lack of sodium in the organism, on the contrary, stimulates secretion of aldosterone, and as a result there is increased reabsorption of sodium in the renal tubules. Aldosterone also reduces the elimination of sodium by the sweat glands: in that way it can prevent loss of sodium through profuse sweating due to overheating.

The amount of aldosterone secreted depends not only upon the absolute content of sodium in the blood plasma and tissue fluid, but also upon the ratio of the concentrations of sodium and potassium ions. Evidence of this is provided by the fact that an increase in aldosterone secretion occurs not only with a deficiency of sodium ions but also with an excess of potassium ions in the blood, while inhibition of secretion may be encountered with an insufficient potassium content. Thus the sodium and potassium ions have an opposite effect on the processes of mineralocorticoid secretion. The influence of alterations in blood potassium on the cells of the adrenal cortex, however, is much weaker than that caused by variations in the sodium level.

The volumes of tissue fluid and blood plasma are also factors influencing the secretion of mineralocorticoids. An increase inhibits aldosterone secretion and leads to elimination of sodium, and consequently of the water combined with it.

The activity of aldosterone secretion is regulated not by the direct action of sodium and potassium on the adrenal cells, but through the hypothalamic region. Destruction of the hypothalamus suppresses the dependence of the internal secretion of mineralocorticoids upon the sodium, potassium and water level of the body and causes

a sharp inhibition of this secretion; but with denervation or transplantation of the adrenals the regulatory influence of the hypothalamus on mineralocorticoid secretion persists, and remains even after removal of the pituitary gland. The hypothalamic region exercises control over aldosterone secretion through the fibres of the vegetative nervous system and by way of humoral pathways.

**Glucocorticoids** (*hydrocortisone, corticosterone, and cortisone*) influence carbohydrate, protein, and fat metabolism. Hydrocortisone is the most active.

Glucocorticoids owe their name to their ability to raise blood-sugar level by stimulating the formation of glucose in the liver. It is supposed that this is accomplished by acceleration of the deamination of amino acids and conversion of their nitrogenfree residues to carbohydrates; it may even be attended by an increase of glycogen in the liver, which distinguishes its effect from that of adrenaline (injection of which increases blood-glucose content and reduces the glycogen reserve in the liver).

The administration of glucocorticoids considerably intensifies the breakdown of tissue proteins and inhibits their synthesis, so that their total amount in the tissues is reduced, though the quantity of protein required for the specific functioning of the organs and tissues (for example, the proteins responsible for muscular contraction) remains unaltered.

The intensified protein breakdown results in an increase of amino acids in the blood, which are utilized in the liver and partly converted to glucose and glycogen. The glucocorticoids also promote fat metabolism stimulating the mobilization of fat from fat depots and thus contribute to an intensification of energy metabolism. Glucocorticoids also influence constructive metabolism and promote restorative and reparative processes.

Glucocorticoids are not vitally essential hormones and their absence does not cause immediate death of the organism; but a deficiency lowers its resistance to various harmful influences, so that infections and other unfavourable factors are poorly withstood and quite often prove fatal.

Glucocorticoids inhibit the production of antibodies (p. 81) and lower the bodily reactions encountered in pneumonia, rheumatic fever, and certain other diseases. Their clinical use in rheumatic fever, allergic conditions, and other ailments is founded on this. Glucocorticoids are known as *anti-inflammatory hormones* because they suppress the development of inflammations. The mineralocorticoids, on the contrary, promote retention of sodium and water, thus contributing to the development of oedema and other manifestations of inflammatory reactions, for which reason they are known as *pro-inflammatory hormones*.

**Factors that influence the intensity of glucocorticoid production.** Output of glucocorticoids increases in pain, injury, blood loss, over-heating, over-cooling, certain poisonings, and severe mental stress. As already mentioned, in these conditions there is a reflex increase in the secretion of adrenaline by the adrenal medulla. Adrenaline enters the blood and acts upon the hypothalamus, causing certain of its cells to form substances that promote secretion of the adrenocorticotrophic hormone by the anterior pituitary lobe. This hormone is a factor stimulating the production of glucocorticoids in the suprarenal glands. Removal of the pituitary gland results in atrophy of the cortical fascicular zone and a sharp drop in production of glucocorticoids.

The condition that results from the action of a number of unfavourable factors and leads to an increase in secretion of the adrenocorticotrophic hormone and, consequently, of glucocorticoids, has been designated *stress* by Selye. He distinguishes three stages or phases in its development: 1) the phase of "alarm reaction", which occurs when the harmful factor begins to act and large amounts of the adrenocorticotrophic hormone and glucocorticoids are released; 2) the phase of resistance, when the increased amount of glucocorticoids circulating in the blood leads to the development of resistance to the harmful effects; 3) the phase of "exhaustion" during which the adrenals no longer produce sufficient glucocorticoids (which Selye considers protective or adaptative hormones) and the condition of the organism deteriorates.

There is a certain community of functional importance between the secretions of the adrenal medulla and cortex. The hormones produced are responsible for increasing defence reactions to the effect of extraordinary factors that threaten the normal condition of the organism or to "emergencies". The medulla secreting adrenaline contributes to an intensification of active, motor reactions, while the cortex, whose activity is stimulated by the adrenaline through the hypothalamus, liberates hormones that intensify internal factors of body resistance.

It should be mentioned, however, that the intensification of body resistance depends upon a very large number of factors and cannot be attributed solely to the processes stimulated by glucocorticoids.

**The sex hormones of the adrenal cortex, androgens and oestrogens,** play an extremely important role in the development of the genital organs in childhood, i. e. at that stage of ontogenesis when the internal secretion of the sex glands is still insufficient. After puberty they are of small significance to the human organism. In old age, however, after the internal secretion in the sex glands has ceased, the adrenal cortex again becomes the sole source of androgens and oestrogens.

## THE SEX GLANDS (GONADS) GENERAL

The sex glands are not only the site where sex cells (spermatozoa and ova) are formed, but also have a function of internal secretion, discharging sex hormones into the blood. These hormones fall into two groups: the *male sex hormones* or *androgens* (Gr. *andros* man), and *female sex hormones* or *oestrogens* (*oestrus*, the period of ovarian hormonal activity or the period of heat). Both types are produced in the male and female gonads, but in different amounts, which can be determined from the urine, in which they are eliminated from the body. The daily portion of male urine contains between three and ten micrograms of androgens and between five and fifteen micrograms of oestrogens; their daily urinary excretion in females is between three and ten micrograms and 18 and 36 micrograms respectively.

The physiological role of the sex hormones consists in ensuring the sexual activity of the organism. They are necessary for sexual maturation, i. e. for the development of the organism and its genital apparatus that makes the sexual act and reproduction possible. They are responsible for the development of *secondary sex characters*, i. e. of peculiarities of the sexually-mature body that are not directly associated with sexual activity but are specific features distinguishing the male and female organisms. The sex hormones play a major role in the onset of the sex cycles in the female organism, ensure a normal course of pregnancy, and prepare the organism to feed the newborn.

### CHANGES ARISING FROM DEFICIENCY OF ENDOCRINE SECRETION BY THE SEX GLANDS

The removal of the sex glands is known as *castration*. The operation is performed not only on animals, but is also indicated as a therapeutic measure in certain human diseases.

The custom of castrating men and boys to serve as eunuchs (of the harem) used to be common in certain Mohammedan countries in the East. Up to the middle of the last century in Western Europe boys who sang in the papal choir were castrated to retain their treble voices. In pre-revolutionary Russia castration was common among members of the fanatic religious sect of skoptsi.

Castration does not completely suppress production of sex hormones in the organism. The blood and urine continue to receive androgens and oestrogens from the adrenal cortex, but in much smaller amounts. Deficiency of the sex hormones gives rise to a number of characteristic changes. When castration is performed long before puberty sexual maturation is arrested; the penis, the prostate, the vagina, and the uterus do not reach maturity and even

undergo retrogressive changes; the secondary sex characters do not develop. If castration is carried out after puberty the retrogressive changes in the genital apparatus are less marked, and some secondary sex characters are retained; those that persist are called *independent sex characters*, and those that disappear *dependent* (Zavadovsky).

The structure of the human skeleton is an independent sex character since the skeleton of a man or woman castrated after puberty retains its specific sex features. The dependent male sex characters are a beard, a low pitch of the voice, and a growth of hair spreading over the pubis and upwards along the middle abdominal line; in females the dependent sex character is the development of the mammary glands. These characters either undergo regression or disappear completely following the castration of mature men or women. Castration in early age produces *asexual characters*. In males these are the absence of a beard, a treble voice, a more pronounced layer of subcutaneous fat, and a horizontal border to the pubic hair, which are characteristic not only of castrated males, but also of normal females. These asexual characters, however, must not be confused with the secondary characters of the female sex; since they do not depend on the internal secretion at the sex glands. Limbs that are unusually long due to delayed ossification of the cartilaginous zones in the long bones are other human asexual characters. This symptom is absent in individuals who have been castrated after the period of growth had ended, but is sharply manifest when castration had been performed at an early age and in eunuchism, a disease caused by a deficiency in sex hormones in childhood.

Under normal conditions both the male and the female sex hormones are formed in the organism of each sex. Their proportions, however, change with the type of dysfunction of the ovaries and testes, encountered in humans known as *intersexuality*; it may be displayed in men by the existence of certain features (physical and psychic) characteristic of women, and in women, by the presence of certain male features.

A slight degree of intersexuality is quite frequently encountered and is not regarded as pathological. Sharply pronounced intersexuality rarely occurs. Even rarer is *hermaphroditism*, a condition marked by the presence of a testis in one side of the body, and an ovary in the other.

#### THE SITE OF SEX HORMONE FORMATION

Ligation of the spermatic cords in males is followed by degeneration of the seminiferous tubules, which are replaced by connective tissue; the accumulations of interstitial-tissue cells that lie between them, do not, however, undergo degeneration and even proliferate;

the males retain their secondary sex characters. It is supposed, on basis of such experiments, that the male sex hormone *testosterone* and, according to the latest data, oestrogen as well, is formed in the interstitial tissue. For that reason this tissue in the testes is known as the *puberty gland*. Some data indicate that the epithelium of the seminiferous tubules is also concerned in the production of androgens, among which testosterone, already mentioned, is the most active.

The oestrogens (*oestrone*, *oestriol*, and *oestradiol*) are formed in the ovaries in the granular layer (stratum granulosum) of the follicles and graafian vesicles and in their internal sheath (theca interna). Androgens are also produced in the ovarian structures.

Experiments using labelled atoms have demonstrated that the sex hormones are synthesized in the testes and ovaries from cholesterol and deoxycorticosterone, which is secreted by the adrenal cortex.

The hormone responsible for the normal course of pregnancy, *progesterone*, is produced in the ovarian corpora lutea which develop in place of the ruptured graafian vesicles (after they have ruptured and discharged their ova).

#### CONTROL OF GONADAL ACTIVITY

The activity of the sex glands is regulated by the nervous system and by hormones secreted by the pituitary and pineal (epiphysis cerebri) glands.

Like all other endocrine glands the ovaries are richly supplied with both efferent and afferent nerves. Their reflex regulation, however, has not yet been sufficiently studied.

It is known that the central nervous system has a significant role in ensuring a normal sex cycle. Strong emotions, like fright and deep grief, may impair the cycle or even suppress menstruations for a more or less long period (*emotional amenorrhoea*).

It has been established that nervous regulation of the sex glands may be effected through reflex changes in the internal secretion of the pituitary gland. Evidence of this is provided by the following facts. In rabbits the sexual act stimulates *ovulation* (the discharge of an ovum from the graafian vesicle) by reflex augmentation of the secretion of the pituitary hormones. The stimulation of ovulation under the influence of light encountered in certain birds also depends upon the intensification of pituitary activity.

The gonadotrophic hormones produced in the anterior pituitary lobe (p.403) have a major role in the control of gonadal activity. Their introduction into a growing organism accelerates and promotes development of the genital apparatus and secondary sex characters through stimulation of the endocrine function of the gonads.

The anterior lobe of the pituitary secretes three gonadotrophic hormones: the follicle-stimulating hormone, the luteinizing hormone, and prolactin. In females, the *follicle-stimulating hormone* promotes the development of follicles in the ovaries and their conversion to graafian vesicles, while in males it promotes the development of seminiferous tubules (*tubulae seminiferae*) in the testes and accelerates spermatogenesis (i. e. the production of spermatozoa) and the development of the prostate. The *luteinizing hormone* stimulates development of the endocrine elements in the testes and ovaries and in that way activates the formation of the sex hormones (androgens and oestrogens). It determines ovulation in the ovary and the formation of the corpus luteum which produces the hormone *progesterone* in place of the ruptured graafian vesicle. *Prolactin*, or the *luteotropic hormone* of the pituitary, stimulates production of progesterone in the corpus luteum and lactation.

The gonadotrophic hormones are of essential importance in sexual maturation. The development of the sex glands in immature animals is delayed after removal of the pituitary, and they remain underdeveloped. The genital apparatus (the penis, prostate, vagina, uterus, and oviducts) are also underdeveloped. Spermatozoa are not formed in the testes, while the ovarian follicles do not reach maturity and are not transformed into graafian vesicles.

Removal of the pituitary from mature animals is followed by atrophy of the seminiferous tubules and interstitial (puberty) tissue in the testes, and disappearance of graafian vesicles and corpora lutea from the ovaries with atrophy of their follicles. Transplantation of the pituitary gland to such animals restores the normal state of their sex glands.

An effect contrary to that exerted on the activity of the genital apparatus by the pituitary is produced by *melatonin* (p.409), a hormone secreted by the pineal body, which inhibits the development and activity of the sex glands.

#### SEXUAL MATURATION

The process of sexual development in man may be divided into five stages: childhood, adolescence, youth, sexual maturity, and the stage of diminution of sexual activity.

The stage of *childhood* lasts until the age of ten in boys and eight in girls, on the average. At this time the testicular seminiferous tubules of boys are narrow and not very convoluted, and have only a single layer of poorly-differentiated germinal epithelial cells; the interstitial tissue is little developed. In girls the ovarian *primordial*, i. e. *primary*, *follicles* which have already been formed in the embryonal stage, continue to grow, but very slowly. Few of the follicles have a membrane and there are no graafian vesicles. The urine of

both boys and girls contains slight but equal amounts of androgens and oestrogens, which are mainly formed in the adrenal cortex.

The *adolescent stage* occurs in boys between ten and fourteen, and in girls between nine and twelve. The seminiferous tubules develop rapidly during this period and become extremely convoluted and twice as wide. The number of epithelial layers increases; spermatocytes, i. e. cells that are the immediate precursors of spermatozoa, appear along with spermatogonia. The interstitial tissue proliferates. In the ovaries the follicles grow rapidly and those with membranes increase in number; there are also more graafian vesicles which form due to accumulation in the follicles of a viscid follicular fluid, which is surrounded by the epithelium that forms the granular layer of the follicle (*stratum granulosum*). The ovum and the epithelial cells surrounding it form a cone-shaped projection pointing toward the centre of the vesicle. The amount of androgens and oestrogens in the urine increases at this stage; the urine of boys contains more androgens, and that of girls more oestrogens.

The *stage of youth* (between fourteen and eighteen in boys and thirteen and sixteen in girls) is marked by rapid development of secondary sex characters. At this stage boys first become capable of the sexual act, then of ejaculation (expulsion of the semen), and lastly of fertilization. In girls there are variations in the oestrogen content of the blood and urine at first at indefinite intervals, but later at periods corresponding approximately to those of the sex cycle of adult women. These variations provide evidence of the developing periodic activity of the endocrine glands, peculiar to women and controlling the female sex cycle. About eighteen months after the appearance of this periodic endocrine activity the first ovulation, i. e. rupture of the most mature graafian vesicle and liberation of its ovum, occurs during one of the routine rises in urinary oestrogen content, and is followed in a few days by the first menstruation. The sex cycles are irregular in the first few months and are often non-ovulatory, i. e. menstruation is not preceded by rupture of a graafian vesicle. *Sexual maturity* is attained only when the sex cycles become quite regular and most of them are ovulatory.

In *advanced age*, usually after forty-five or fifty in women and after sixty in men (in some cases much later), the *climacteric*, i. e. loss of sexual activity, is established gradually. The sex cycles in women become more irregular, non-ovulatory cycles occurring more frequently, and then cease completely, with cessation of menstruation (*age amenorrhoea*). The follicles disappear completely from the ovaries. In men this period is marked first by loss of motility of the spermatozoa and resulting loss of fertility, then by loss of ability to ejaculate, and lastly by loss of ability to perform the sexual act. The seminiferous tubules, the testicular interstitial tissue, and

the prostate become atrophied. The age periods mentioned above vary widely with the individual and depend upon mode of life, the diseases suffered, climate, etc.

#### THE FEMALE SEX CYCLE

With the onset of puberty in women ovulation occurs periodically. The sex cycle lasts for twenty-seven or twenty-eight days, and is divided into four periods: 1) *pre-ovulation* (praeoestrus), 2) *ovulation* (oestrus), 3) *post-ovulation* (metaoestrus), 4) the period of rest (dioestrus). Each period is characterized by definite changes in the organism (Fig. 108).

**The pre-ovulation period.** In this period the organism is prepared for pregnancy. In many animal species with seasonal mating it is at the same time the period during which the genital apparatus of the female is prepared for the sexual act, when she comes into heat and allows the male to perform this act.

The following changes are encountered in women: the uterus becomes enlarged and filled with blood while its mucous coat and glands proliferate; the peristaltic contractions of the fallopian tubes

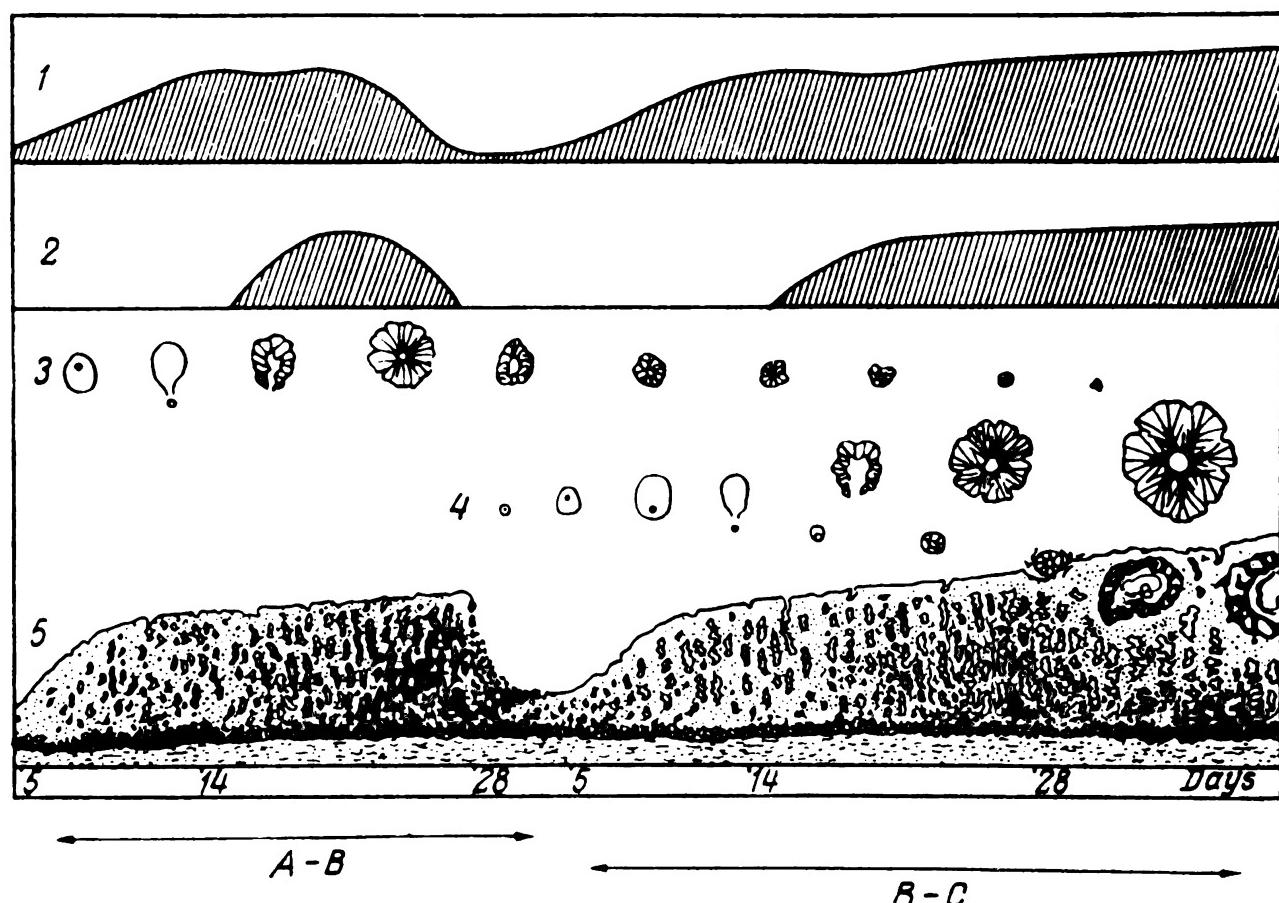


FIG. 108. Diagram of changes occurring in the ovary and mucous coat of the uterus in a normal menstrual cycle (A-B) and in a menstrual cycle terminating in pregnancy (B-C) (after Schroeder)

1 — blood oestrogen level; 2 — blood progesterone level; 3 — follicle and corpus luteum of cycle A-B; 4 — follicle and corpus luteum of cycle B-C; 5 — changes in the mucous coat of uterus. The figures at the bottom of the diagram indicate the days of the cycle

and uterine muscular coat become more active and frequent, the vaginal mucosa proliferates and the number of desquamating epithelial cells in the vaginal mucus increases. These changes are caused by increased secretion of the follicle-stimulating hormone of the pituitary.

This hormone also acts upon immature female animals; if increasing amounts of an extract of the anterior pituitary lobe or follicle-stimulating hormone are introduced into them day after day changes in the uterus and vagina characteristic of praekoestrus and oestrus occur. If the pituitary gland of mature female animals is removed surgically at the onset of praekoestrus, further development of pre-ovulation changes in the uterus and vagina ceases and oestrus does not occur.

The amount of gonadotrophic hormones in the anterior pituitary lobe increases during praekoestrus and oestrus and drops sharply after ovulation.

All pre-ovulation changes are caused by the gonadotrophic hormones of the pituitary through their influence on ovarian endocrine activity. The production of oestrogens in the ovaries is intensified at this time; they stimulate enlargement of the uterus and proliferation of its mucosa and of the vaginal mucosal epithelium, and promote the contraction of the uterus and fallopian tubes. The administration of increasing amounts of oestrogens over several days produces typical pre-ovulation changes in the uterus and vagina of women who have had their ovaries removed for therapeutic reasons.

In a normal organism the gradually increasing amount of the follicle-stimulating hormone accelerates complete maturation of the most prepared graafian vesicles. Its surface ruptures and the ovum is released, in other words, *ovulation* occurs.

The period of ovulation begins as soon as the graafian vesicle ruptures, and the ovum discharged moves along the fallopian tube into the uterus. Fertilization of the ovum occurs while it is passing along the tube. The fertilized ovum, reaching the uterus, becomes attached to its mucosa. With that the sexual cycle is interrupted and pregnancy sets in. After discharge of the ovum a corpus luteum begins to form at the site of the ruptured graafian vesicle, that produces not oestrogen, but the hormone *progesterone*. That does not mean, of course, that the secretion of oestrogen ceases in the ovaries; it continues as before in the other numerous maturing follicles.

The ovum liberated from the ruptured vesicle is directed into the fallopian tube by movements of the ciliate epithelium lining its fimbriae overhanging the ovary. The contractions of the smooth muscles of the tube are intensified at the same time by the influence of the increased oestrogen content of the blood. Thus the ovum is initially pushed quite quickly through the tube, but with the gradual

increase in progesterone secreted by the corpus luteum forming in the ovary, the peristaltic contractions become weaker and less frequent since progesterone counteracts the stimulating effect of oestrogen on the muscular contractions of the tubes and uterus. On the whole, it takes about seventy-two hours to drive the ovum along the tube to the uterus. If it is not fertilized in that time the post-ovulation period sets in.

**The post-ovulation period.** *Menstruation* occurs in women in this period; in animals, however (with the exception of primates), it does not occur.

The unfertilized ovum, having entered the uterus, remains viable there for several days and then dies. At the same time, secretion of gonadotrophic hormones declines under the influence of progesterone. Reduction in the amount of follicle-stimulating hormone from the pituitary brings about a decrease in the production of oestrogens in the ovaries; consequently the factor causing and maintaining the pre-ovulation changes in the tubes, uterus, and vagina is abolished. The decrease in the luteinizing hormone leads to atrophy of the corpus luteum with its subsequent replacement by a connective-tissue cicatrix, owing to which the ovarian production of progesterone ceases. The pre-ovulation changes in the uterus, tubes, and vagina are diminished.

As the result of the fall in the amount of ovarian hormones in the blood, tonic contractions of the uterus are activated and its mucosa is cast off. Shreds of the mucosa are discharged together with blood from the menstrual bleeding that occurs; when the bleeding ends the mucosal coat of the uterus quickly regenerates.

As soon as the post-ovulation period is completed, the dioestrus begins and is followed by the pre-ovulation period of a new cycle.

#### HORMONAL CHANGES FOLLOWING FERTILIZATION

In women, fertilization of the ovum can take place only in the first two days after ovulation, that is, while the egg is still in the fallopian tube. On the third day it becomes covered with a protein membrane that prevents the penetration of spermatozoa. Thus it follows that the sexual act can terminate in pregnancy only if performed shortly before ovulation (not more than five to seven days earlier, in the opinion of most researchers), so that there are still live fertile spermatozoa in the genital passages, or within the first two days following ovulation. Passage of spermatozoa from the vagina into the uterus and further into the fallopian tubes and fertilization are facilitated during oestrus by the mucus secreted by the uterine, and tubal mucosa during praeoestrus and oestrus being more acid than that secreted during the post- and interovulation periods; with a shift in the reaction of the medium toward

acidity the motility of the spermatozoa and their capacity of penetrating an ovum are increased.

After the fertilized ovum has entered the uterus, it moves freely in the uterus for a few days and then becomes implanted in the uterine mucosa (Fig. 108). Implantation is facilitated by the proliferation of mucous membrane that begins in the pre-ovulation, and by the increased sensitivity of this mucosa to contact induced by the action of the progesterone secreted by the corpus luteum on the uterus.

Progesterone also promotes implantation because it inhibits contraction of the uterine muscles and in that way allows the ovum to be in contact with any one spot on the mucosa for long enough for implantation to occur.

With implantation the production of gonadotrophic hormones in the anterior pituitary lobe does not diminish; on the contrary, the luteotropic hormone is formed in even greater amounts. The secretion of gonadotrophic hormones is apparently stimulated through the influence of nerve impulses that begin to reach the central nervous system from the uterus as soon as an ovum is implanted there. As a result of the increased production of the luteinizing hormone the corpus luteum in the ovary is not replaced by scar tissue but grows (*corpus luteum of pregnancy*) and accordingly secretes greater amounts of progesterone.

By inhibiting uterine contractions progesterone promotes preservation of pregnancy. Experiments on monkeys have shown that removal of the corpus luteum in the first half of pregnancy causes abortion.

Of great importance is the stimulating effect of progesterone and oestrogen on the development of the mammary glands. This has been established in experiments on male animals; the administration of oestrogen and progesterone over a quite long period causes their mammary glands to develop to such an extent that they become capable of secreting milk. The data obtained indicates that oestrogen stimulates development of the mammary ducts, and progesterone, development of the glandular lobes. In addition *prolactin*, a hormone produced in the anterior lobe of the pituitary, contributes significantly to the secretion of milk; it does not influence the development of the mammary glands but stimulates lactation in the already developed glands.

A hormone that causes relaxation of the pubic symphysis, and for that reason called *relaxin* (L. *relaxare* to loose), has been extracted from the corpus luteum, and in particularly large amounts from the placenta. Through its action the bone structures of the small pelvis move apart at the end of pregnancy, which facilitates delivery.

## THE PLACENTAL HORMONES

The placenta also takes part in the endocrine control of pregnancy, secreting *oestrogen*, *progesterone*, and *chorionic gonadotrophin*. For that reason, such operations as removal of the pituitary gland or the ovary, if performed on an animal during the second half of pregnancy, that is, when the placenta is already well developed and produces an adequate amount of these hormones, does not cause abortion; the placental hormones are quite capable of replacing the respective hormones of the pituitary gland or the ovaries.

Chorionic gonadotrophin is identical in its action with the pituitary luteinizing hormone. It is excreted in large amounts in the urine during pregnancy, and that fact is utilized to diagnose pregnancy by means of an extremely simple test. Five or ten millilitres of urine are introduced subcutaneously into the back of a male frog; spermatozoa will appear in its cloaca within two hours if gonadotrophin is present in the urine.

## THE PITUITARY GLAND

The pituitary gland, or *hypophysis cerebri* is a complex endocrine gland consisting of three parts, the anterior lobe, the intermediate part, and the posterior lobe.

### STRUCTURE OF THE ANTERIOR PITUITARY LOBE

The anterior lobe, or the *adenohypophysis*, consists of three types of cells: namely, chief, or chromophobe (55 or 60 per cent), chromophile or acidophile (30 to 35 per cent), and basophile (5 or 10 per cent). Chromophobe cells do not apparently produce hormones and are the precursors of the chromophile cells. The basophile cells produce the adenocorticotropic, thyrotrophic, and gonadotrophic (follicle-stimulating and luteinizing) hormones. The acidophile cells produce the growth hormone and prolactin.

All the hormones secreted by the anterior lobe are proteins.

### THE GROWTH HORMONE

The *growth hormone* (the *somatotrophic hormone*, or *somatotrophin*) stimulates the growth of young animals (Fig. 109).

The exact chemical structure of this hormone is not yet known. In man its molecule consists of a single peptide chain containing 240 amino acids (molecular weight about 27,000), in cattle it is made up of two peptide chains with 369 amino acid residues (molecular weight approximately 46,000).

Somatotrophin exerts an effect on a number of metabolic processes occurring in the organism. It increases protein synthesis

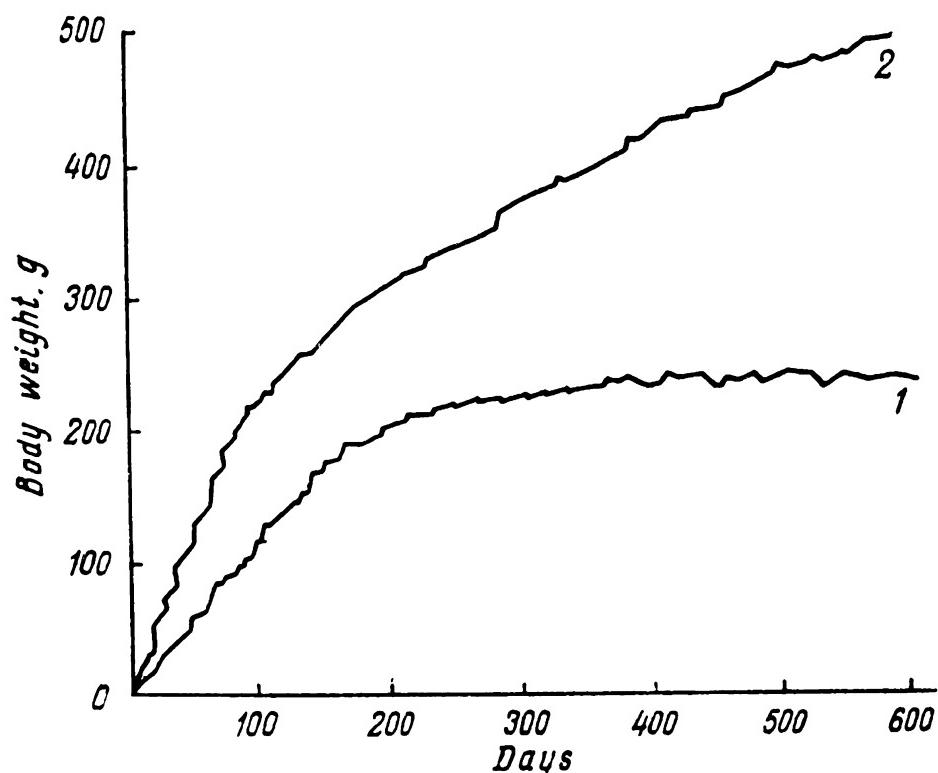


FIG. 109. Gain in weight in a normal rat (1) and in a rat given daily injections of the growth hormone (2)

in all the cells of the body and their content of ribonucleic acid and reduces the amino acid content of blood and the amount of nitrogen excreted in the urine.

The mechanisms underlying the stimulating effect of the somatotrophic hormone on protein synthesis in the cells have still not been sufficiently studied. It is known that it requires the presence of carbohydrates and insulin. The action of the hormone is inhibited in pancreatectomized animals and in animals whose diet is deprived of carbohydrates. Its injection stimulates the secretion of insulin in young animals, but in adult animals no such effect is produced, the pancreatic islets degenerate, and diabetes develops.

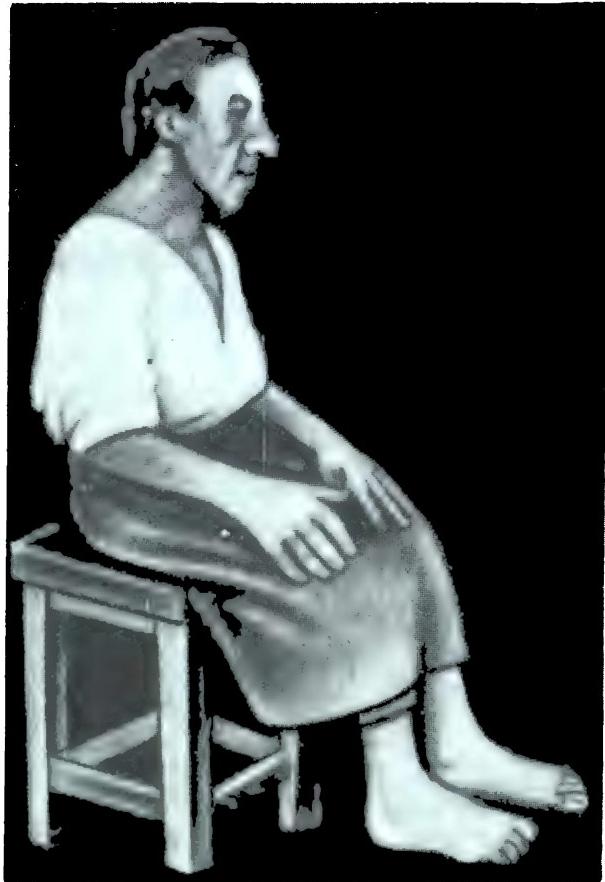
Administration of the growth hormone activates the mobilization of fat from depots and its utilization in energy metabolism, which increases fat expenditure and a rise in the level of acetone and ketone bodies in the blood and their elimination in the urine.

The somatotrophic hormone is secreted continuously throughout life.

**Changes occurring through deficient or excess production of the growth hormone.** The manifestations of a deficiency differ according to the age of the organism. A sharp retardation of growth occurs in early childhood and the individual remains a dwarf throughout life (*hypophysial, or pituitary, dwarf*) (Fig. 110). The body build of such individuals is relatively proportional; their hands and feet, however, are small, the fingers are thin, ossification of the skeleton



**FIG. 110.** Pituitary dwarfism and gigantism. Left, 14-year-old male pituitary dwarf (height 100 cm); right, pituitary gigantism in a boy aged thirteen years and ten months (height 187 cm); centre, a boy of the same age and normal height (148 cm) (after Shereshevsky)



**FIG. 111.** Acromegaly. Enlargement of the nose, lower jaw, hands, and feet. Necropsy showed that the pituitary gland was abnormally large, forming a tumour the size of a cherry (after Müller)

is retarded, the genital organs are infantile, the secondary sex characters are poorly developed, and the hair is soft and silky as in children. Such patients withstand infectious and other diseases poorly and many die young. Men suffering from this disease are impotent, i. e. are unable to perform the sexual act, while women are sterile, i. e. are unable to conceive.

Excess production of the growth hormone from early childhood results in *gigantism*, the individual attaining a height of 240 to 250 centimetres and a weight of 150 kilograms. But if the increase in its production occurs in adult life when the growth of the body has already on the whole been completed, only those parts still capable of growth enlarge, viz., the fingers and toes, hands and feet, nose and lower jaw, and tongue, and the thoracic and abdominal organs. This disease is known as *acromegaly* (Gr. *akron* extremity, *megale* great) (Fig. 111). Disorders in the functions of endocrine glands controlled by the hormones of the anterior pituitary lobe, in particular insufficiency of internal secretion in the gonads, are encoun-

tered in acromegalic patients and pituitary giants. An insufficiency of pancreatic insular tissue is also observed in acromegaly, giving rise to diabetes mellitus. Acromegaly is usually caused by a tumour of the anterior pituitary lobe.

#### THE GONADOTROPHIC HORMONES

*Prolactin*, or the *luteotrophic hormone*, produced by the acidophil cells of the anterior lobe is a protein with a molecular weight of 25,000 to 30,000. It is broken down by the enzymes in the alimentary tract and for that reason has to be injected either subcutaneously or intravenously. This hormone stimulates production of milk in the mammary glands following their exposure to the effect of oestrogens and progesterone; it also stimulates the development of the corpus luteum.

The removal of the hypophysis from nursing rats suppresses *lactation*. Injection of prolactin not only activates lactation in nursing females but also causes a slight secretion of milk in young females if they have reached maturity.

Prolactin induces secretion of milk in adult females even if they have been castrated. Its injection can even cause lactation in males, but they must be first treated for some time with oestrogen and progesterone because their mammary glands are in a rudimentary state and cannot secrete milk without artificially induced development of the gland tissue. Injection of prolactin leads to development of the maternal instinct even before maturity.

Prolactin causes a decrease in the utilization of glucose by the tissues, leading to an increase in blood glucose, i. e. has an effect similar to that of somatotrophin, though much weaker. Its secretion is stimulated reflexly by the centres lying in the hypothalamic region. The reflex arises on stimulation of the receptors in the nipples during sucking, the stimulation exciting the hypothalamic nuclei, which influences pituitary activity humorally by neurosecretion.

In distinction from prolactin, which is formed by the acidophile cells, the other two gonadotrophic hormones, the *follicle-stimulating* and the *luteinizing*, are produced by the basophile cells of the anterior lobe. Preparations of these hormones, which are glucoproteins with a molecular weight around 30,000, have been derived from the pituitary of various animals. They are inactivated by exposure to amylase, which indicates that the active group in these hormones contains a polysaccharide.

The physiological effects produced by the follicle-stimulating and the luteinizing hormones have already been discussed (p.394). They are due to the action of these hormones on the sex glands of males and females, i. e. to stimulation of the development of the

puberty gland and follicles and to the formation of sex hormones in them.

The introduction of gonadotrophic hormones into castrated animals does not produce the characteristic physiological effects encountered in sexually immature animals. This is convincing evidence that the acceleration of sexual maturation (with enlargement of the genital organs and early appearance of secondary sex characters) in immature animals following regular injections of the gonadotrophic hormones results from their action on the gonads. The direct cause of these effects is the action of the hormones produced by the gonads and not the action produced by the pituitary gonadotrophins themselves. It is only the enlargement of the prostate, induced by injections of the follicle-stimulating hormone not only in normal males but also in castrated ones, that is the result of the direct stimulating effect of this hormone.

The intensity with which the gonadotrophic hormones are secreted depends upon the reflex influence of the sexual act and the humoral influence of the testicular and ovarian hormones, and upon various environmental factors. The production of gonadotrophic hormones in man is influenced by psychic experiences. It was noticed during World War II, for instance, that the fear caused by air raids or imprisonment in a concentration camp caused drastic disorders in the secretion of gonadotrophic hormones and led to cessation of menstrual cycles.

#### THE THYROTROPHIC HORMONE (THYROTROPHIN)

The *thyrotrophic hormone* secreted by the basophile cells of the anterior pituitary lobe is a glucoprotein with a molecular weight between 26,000 and 30,000. It stimulates secretion of the thyroid hormones. The mechanisms responsible for this stimulation are multiform. Thyrotrophin activates proteases and in that way increases the breakdown of thyroglobulin in the thyroid gland, which leads to an intensified discharge of thyroxine and tri-iodothyronine into the blood. It also promotes accumulation of iodine in the thyroid, and in addition stimulates the activity of the secretory cells in that gland, and increases their number.

Injection of the thyrotrophic hormone causes enlargement of the thyroid, while removal of the pituitary gland leads to its underdevelopment in young animals and to its reduction and partial atrophy in adults. Basal and protein metabolism decreases in hypophysectomized animals, but may be increased again by the introduction of thyroxine, transplantation of the pituitary body, or injection of the thyrotrophic hormone. The introduction of thyroxine normalizes basal and protein metabolism because it compensates for the deficient production of the hormone in the animal's atrophied thyroid; transplantation of the pituitary or injection

of the thyrotrophic hormone bring metabolism back to normal because they cause enlargement of the thyroid (which also becomes atrophied with lack of this hormone).

Animals treated daily with sufficiently large doses of the thyrotrophic hormone over a long period of time display symptoms resembling Basedow's disease in man.

Thyrotrophin is secreted continuously in small amounts. Its secretion is stimulated by the hypothalamus whose nerve cells produce physiologically active substances that activate the anterior pituitary lobe; it also depends upon the level of thyroid hormones in the blood, is inhibited when that level is sufficient, but activated when it is deficient. Thus there is a feedback mechanism here.

With cooling of the organism secretion of thyrotrophin is intensified and the production of hormones in the thyroid gland increases, and in consequence heat production is raised. If the organism is repeatedly exposed to the effect of cooling thyrotrophin secretion is also stimulated by the action of signals that precede the cooling, owing to the formation of a conditioned reflex. Hence it follows that the cerebral cortex can influence secretion of the thyrotrophic hormone, a circumstance that plays an important part in hardening the body, i. e. in raising its resistance to cold by training.

#### THE ADRENOCORTICOTROPHIC HORMONE

The adrenocorticotrophic hormones (ACTH) of various animals differ in both structure and activity. They are polypeptides with a molecule composed of a chain of 39 amino acid residues. Various precursors of ACTH have been isolated from the anterior lobe of the pituitary, which are converted to ACTH on breakdown.

The adrenocorticotrophic hormones cause proliferation of the fascicular and reticular zones of the adrenal cortex and intensify hormone synthesis in them. This effect is also encountered in hypophysectomized animals in which these zones have become atrophied because the organism lacked its own ACTH.

Removal of the hypophysis does not lead to atrophy of the glomerular zone of the adrenal cortex and medulla, which shows that the action of ACTH is specific and involves only the fascicular and reticular zones of the adrenal cortex.

ACTH output by the pituitary is increased by all excessive stimuli that produce a condition of stress in the organism. These stimuli act upon the hypothalamic nuclei both by reflex and by activating secretion of adrenaline in the adrenal medulla; neurosecretion, i. e. the formation of biologically active substances, is thereby increased. Owing to the vascular connection existing between the hypothalamus and the pituitary gland, these substances reach the anterior lobe and stimulate secretion of ACTH, which in turn, by its action upon the

suprarenal glands, causes intensified production of glucocorticoids and thus promotes a raising of resistance to the effect of unfavourable factors.

#### THE PARS INTERMEDIA

In most animals and in man the pars intermedia is isolated from the anterior lobe and fuses with the posterior pituitary. Its hormone, *intermedin*, or the *melanocyte-stimulating hormone*, is secreted together with those of the posterior pituitary.

Intermedin causes darkening of the skin of amphibia (frogs in particular) and certain fishes through dilatation of the melanophores, or pigment cells of the skin, and wider distribution of the pigment granules occurring in their protoplasm. Its significance consists in adaptation of the colour of the body covering to the colour of the surroundings. Intracutaneous injection of intermedin into areas of human skin devoid of pigment leads to gradual development of normal colour. Intermedin apparently also controls skin pigmentation in man.

The secretion of intermedin is controlled reflexly by the effect of light on the retina of the eye. In mammals and man the hormone regulates movement of the cells of the black pigment layer of the retina. When exposed to bright light these cells thrust out pseudopodia by which the excess light rays are absorbed by the pigment and the retina is protected from too intense stimulation.

#### THE POSTERIOR PITUITARY

The posterior lobe of the pituitary body (*neurohypophysis*) consists of cells called pituicytes, which resemble the cells of the neuroglia. They are innervated by fibres passing through the peduncle of the hypophysis, which are processes of the hypothalamic neurones.

**Changes occurring from disturbed secretion of the posterior pituitary.** Hypofunction of the posterior lobe is the cause of *diabetes insipidus*, a condition marked by an enormous discharge of urine (a score of litres or more a day) that contains no sugar, and by strong thirst. Subcutaneous injection of a preparation of the posterior lobe brings the daily amount of urine of sufferers down to normal. Post-mortem examination reveals lesions of the posterior lobe.

**Hormones of the posterior lobe.** Two preparations have been derived from the posterior lobe; one markedly inhibits urine formation and increases blood pressure, the other causes contraction of the uterine muscles. The first is called the *antidiuretic hormone*, or *vasopressin*, and the second *oxytocin*.

The mechanism of the antidiuretic effect of vasopressin consists in intensifying reabsorption of water through the walls of the

collecting tubules. For that reason its administration to animals and man results not only in a decrease in diuresis, but also in a higher specific gravity of the urine.

Vasopressin induces contractions of the smooth muscles of the vessels (the arterioles in particular) and leads to a raising of blood pressure. Hence its name. The pressor effect, however, is of more interest to pharmacology than to physiology, and is encountered only when the hormone is introduced artificially in large doses; the amounts normally secreted only have an antidiuretic effect and do not influence the smooth muscles of the vessels.

Oxytocin stimulates contractions of the smooth muscles of the uterus, in particular at the end of pregnancy. Its presence is indispensable for normal childbirth. Removal of the pituitary gland from pregnant females results in difficult and protracted parturition. Oxytocin is also important in lactation (p. 366).

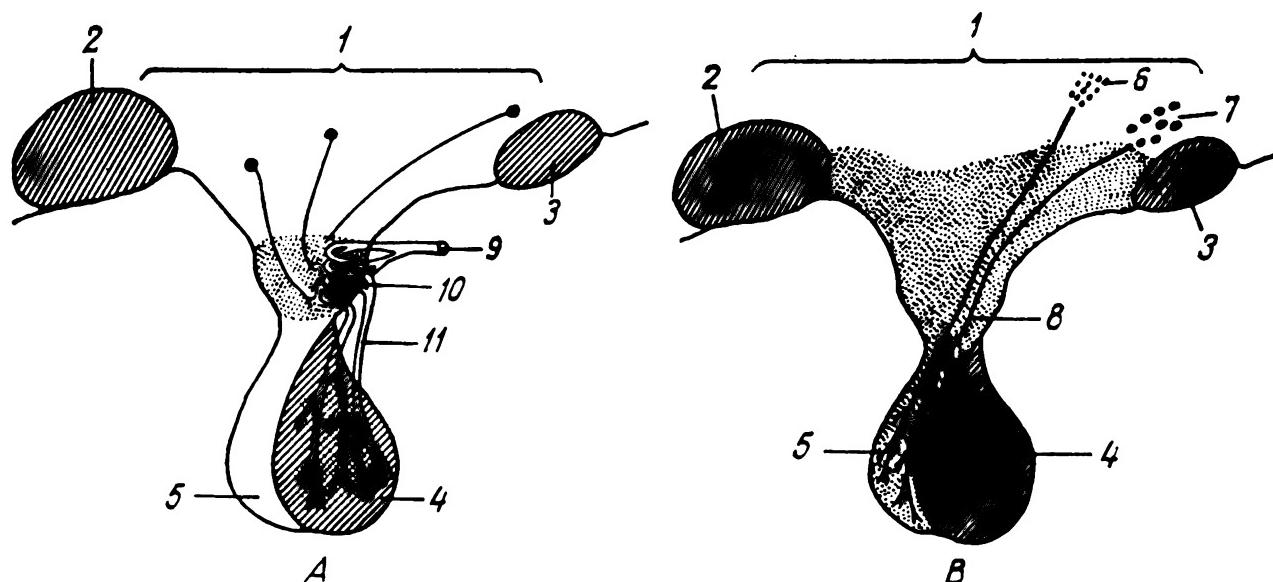
The chemical structures of vasopressin and oxytocin have now been established, and they have been synthesized. It was found that the molecule of each consists of eight amino acids and three molecules of ammonia. They have six amino acids in common, and differ in the remaining two (leucine and isoleucine in oxytocin, phenylalanine and arginine in vasopressin). Thus, unlike the hormones of the anterior lobe, the hormones of the posterior pituitary are not very complex polypeptides.

#### CONTROL OF PITUITARY SECRETION

The internal secretion of the pituitary gland, which controls the function of a number of other endocrine glands (gonads, adrenals, thyroid), is in turn dependent upon the activity of those glands. Thus, deficiencies of androgens and oestrogens and of glucocorticoids and thyroxine in the blood stimulate production of the gonadotrophic, adrenocorticotrophic, and thyrotrophic hormones respectively. On the contrary, an excess of gonadal, adrenal, and thyroid hormones inhibits production of the corresponding pituitary hormones.

Thus the pituitary gland is part of the system of neuro-humoral regulation operating on the principle of feedback and automatically maintaining the hormone production in the glands concerned at the required level. The mechanisms underlying this automatic regulation, and the pathways through which the necessary information is transmitted, are not yet completely clear. The anterior lobe is innervated by branches of the sympathetic nerve, which apparently mainly control the lumina of the vessels and not the secretory activity of the gland cells.

Of great importance in this control are the special features of the blood supply of the anterior lobe, namely that it shares this supply with the hypothalamus. Blood flowing from the capillaries



**FIG. 112. Diagram of the vascular connections between the hypothalamus and anterior pituitary lobe (A) and the nervous connections between the hypothalamus and posterior pituitary (B)**

1 — diencephalon; 2 — mammillary bodies; 3 — optic chiasma; 4 — anterior lobe; 5 — posterior pituitary; 6 — paraventricular nucleus of hypothalamus; 7 — supraoptic nucleus; 8 — hypothalamo-hypophyseal tract; 9 — artery; 10 — primary capillary network; 11 — hypothalamo-hypophyseal portal vein

of the hypothalamic region enters the so-called portal vessels of the pituitary and flows around its cells (Fig. 112 A). In the hypothalamic region these capillaries are surrounded by a network of nerve-cell processes forming peculiar neuro-capillary synapses along them. The products of neurosecretion, i. e. the physiologically active substances formed by the hypothalamic nerve cells, are conveyed through these structures into the blood and then carried directly to the cells of the anterior lobe stimulating their activity. Thus, the internal secretion of the anterior lobe is controlled by the nervous system, i. e. the hypothalamic nuclei, but the regulating influence is transmitted through humoral rather than nervous pathways.

In contrast to the anterior lobe, the posterior pituitary has a direct nerve connection with the hypothalamic nuclei, since the axons of the nerve cells located in them pass through the hypophyseal peduncle and terminate in the posterior lobe (Fig. 112B). The interrelations between the pituitary body and the hypothalamus are not solely the regulatory influence of the latter on the activity of the former. There is evidence that the physiologically active products of hypothalamic neurosecretion that reach the posterior pituitary along the axons terminating in it are the chemical precursors of the pituitary hormones. Thus, the precursors of oxytocin and the antidiuretic hormone are complex protein compounds produced by the hypothalamic cells and conveyed along their axons to the posterior pituitary where they are accumulated in the pituicytes, converted to hormones, and discharged into the blood.

The connection between the cells of the anterior lobe and the hypothalamus is effected quite differently. Hormone production is induced in this lobe by neurosecretions reaching it from the hypothalamic nuclei. It is known that nerve impulses arising under the influence of extraordinary stimuli bring about a condition of stress and stimulate secretion of a biologically active substance, the *corticotrophin-releasing factor*, in the posterior nuclei of the hypothalamus. Similarly secretion of the pituitary gonadotrophic hormones depends upon the liberation of a *gonadotrophin-releasing factor* by the hypothalamic nuclei, while the production of the thyrotrophic hormone is governed by a *thyrotrophin-releasing factor*. The fact that a pituitary gland transplanted to the neck does not secrete these hormones supports this assumption, as does the fact that their production is resumed as soon as it is retransplanted to the region of the sella turcica. Consequently, normal secretion of the hormones requires continuous supply of products of hypothalamic neurosecretion to the pituitary gland.

The feedback mechanism by means of which the levels of the thyroid, adrenal, and gonadal hormones in the blood respectively regulate secretion of the pituitary thyrotrophic, adrenocorticotropic, and gonadotrophic hormones is effected through the nuclei of the hypothalamic region. Thus, the direct action of the thyroid or gonadal hormones on the cells of the anterior lobe does not inhibit production of thyrotrophin or gonadotrophins respectively; but this effect is obtained when these hormones act upon the hypothalamic region, but only if the connections between the pituitary gland and hypothalamus are intact, otherwise inhibition does not occur.

Thus the pituitary body and the hypothalamus are an integral system that regulates the vegetative functions of the organism, both by the secretion of the pituitary hormones, i. e. by way of humoral pathways, and directly by way of the vegetative nervous system, the highest nerve centre of which is the hypothalamic region.

#### THE PINEAL BODY

The functions of the pineal body, or *epiphysis cerebri*, were quite unknown until recently. In the seventeenth century Descartes supposed it to be "the seat of the soul". At the end of the nineteenth century it was discovered that lesions of the pineal body in children are attended with premature pubescence and it was suggested that it was concerned with development of the genital apparatus.

It has now been established that a substance named *melatonin* is formed in the pineal body. This name was suggested because the substance has an active effect on the melanophores. Its action is opposite to that of intermedin, and causes the skin to turn a lighter colour.

In the organism of mammals melatonin acts upon the gonads, delaying sexual maturation of immature animals, and reduction in the size of the ovaries and inhibition of the oestral cycles in adult females.

The secretion of the pineal body varies according to how long the organism stays in the dark or in the light. Exposure to light inhibits its production of melatonin. The seasonal character of the sexual activity of certain animals, and of birds in particular, its increase in the spring and summer, when production of melatonin decreases because the days are longer, are attributed to this phenomenon.

The pineal body also contains much serotonin (p. 411), a precursor of melatonin. Its production, too, increases during the period of most intensive illumination. The secretion of the pineal body is controlled by the sympathetic nervous system. Since the cycle of biochemical processes in the gland reflects the succession of day and night, it is thought that it is a peculiar "biological clock" in the organism.

#### TISSUE HORMONES

Biologically active substances with a specific action are produced not only by the cells of the endocrine glands, but also by specialized cells localized in various other organs. Many of these substances, known as *histohormones*, or *parahormones*, are of a "local" importance as it were, since their influence is exerted not on the organism as a whole, but on processes that regulate the activity of the organ or cell (or even part of it) in which they are formed. The nature of some of them, the way they act, and their physiological significance are discussed in the appropriate chapters; here we shall only give some brief notes on them.

**Hormones of the alimentary tract.** It has already been mentioned that the activity of the alimentary organs is regulated not only by the nervous system, but also by a great many "local" hormones secreted by various parts of the alimentary tract and are of local importance. They include: *gastrin*, *enterogastrin*, *enterogastrone*, *secretin*, *pancreozymin* (*cholecystokinin*), *enterocrinin*, and *villikinin*.

**Hormones that influence the vascular system.** Apart from those already discussed (*adrenaline*, *noradrenaline*, and the pituitary anti-diuretic hormone or *vasopressin*), a number of biologically active substances can produce changes in arterial pressure. Among them is *renin*, which is formed in the juxta-glomerular apparatus of the kidneys and causes the conversion of plasma hypertensinogen to hypertensin, which stimulates contraction of the smooth muscles of the arterioles.

An active substance, *kallikrein*, has been derived from the submandibular salivary gland, lungs, and pancreas of a number of animals;

it is responsible for the breakdown of one of the globulins of blood plasma, with liberation of *kallidin*. Kallidin causes relaxation of the smooth muscles of the arterioles and reduces arterial pressure; in this respect it is an antagonist of noradrenaline.

*Bradykinin*, a polypeptide formed in many cells, also has a vasodilatory effect. It appears in skin exposed to the effect of heat and is one of the factors responsible for dilatation of vessels in response to warming. It is supposed that bradykinin may also produce the sensation of pain, being a stimulator of the pain receptors. A similar action is characteristic of *histamine*, which occurs in the skin when various stimuli, including pain, act upon it, in the stomach during digestion, and in working muscles. The appearance of histamine (along with the formation of carbon dioxide, lactic acid, phosphoric acid, and other metabolites) is one of the factors responsible for dilatation of the arterioles and capillaries in the working muscles, bringing about an increase in their blood supply.

As with bradykinin, histamine contributes by its action on pain receptors to the development of sensations of pain and pruritus. It increases the permeability of the capillary wall and facilitates the passage (transudation) of water and proteins from the plasma into the tissues.

The group of substances that constrict the arterioles and raise arterial pressure includes *serotonin* (5-hydroxytryptamine) which is formed in the nerve tissue, intestine, pineal body, reticulo-endothelial cells, and blood platelets. It has a wide spectrum of activity resembling that of adrenaline. The opinion has been expressed that serotonin is involved in the mediation of nerve impulses in the nervous system.

**Other biologically active substances.** There are a number of other tissue hormones that are concerned with regulation of various physiological processes. For instance, *parotin*, a substance that stimulates the nutrition of cartilaginous tissue and the development of tooth dentin and bone tissue, has been found in extracts of the submandibular gland. There are observations that, until the onset of sexual maturity, the thymus secretes a substance that inhibits the activity of the thyroid and sex glands.

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Boris KHODOROV, D.Sc., heads the Biophysical Research Laboratory of the Vishnevsky Institute of Surgery of the USSR Academy of Medical Sciences. He is an acknowledged specialist in neurophysiology and has done important research in the general physiology of excitable tissues and on conditioned motor reflexes in animals and human beings. He has published seventy-five scientific works.



Professor Grigory KOSITSKY, D.Sc., Corresponding Member, holds the chair of physiology in the Second Medical Institute in Moscow. He is occupied with research in the field of the physiology of circulation and respiration and has suggested a new method of studying coronary circulation and respiration. He has published two monographs and more than 200 papers.



The late Professor Anatoly ZUBKOV, D.Sc., held the chair of physiology in the Kishinev Medical Institute. He was a brilliant lecturer and experienced teacher, and the author of over sixty published works on various problems of the physiology and pathology of the heart and the nervous and endocrine control of functions.